21.10.9 Malignancy-associated renal disease 5041

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21.10.9 Malignancy-associated renal disease 5041 21.10.9 Malignancy-associated renal disease A. Neil Turner ESSENTIALS Malignancies can affect the kidneys by direct invasion, meta- bolic and remote effects of tumour products, deposition of tu- mour products, triggering of immune reactions, and effects of treatment. Particular malignancy-associated renal diseases include the following: Thrombotic microangiopathy—particularly reported for malignan- cies of the stomach, pancreas, and prostate, and also with certain chemotherapeutic agents. Minimal-change nephrotic syndrome—rarely caused by lymphoma. Membranous nephropathy—associated with malignancy, usually of solid organs, in 5 to 11% of cases. Malignant disease is typic- ally advanced and obvious when nephrotic syndrome or heavy proteinuria is recognized. Very few treatable and otherwise sub- clinical tumours are uncovered by investigation in routine clinical practice. Focal necrotizing and crescentic nephritis—may rarely be associated with malignancy, when they are usually antineutrophil cytoplasmic antibody negative. Proteinuria—may be caused by agents that modulate interferons or vascular endothelial growth factors. Introduction Malignant disease may affect the kidney and urinary tract by five broad mechanisms (see Table 21.10.9.1). Acute kidney injury is common in patients with malignancy: in many instances the cause is not specifically related to the malignancy, but it can be, and in many instances several factors combine (Fig. 21.10.9.1). Direct involvement of the urinary tract Solitary kidney tumours in adults are usually caused by renal cell carcinoma (hypernephroma). Bilateral tumours may occur, but multicentric tumours or bilateral tumours in young patients should lead to suspicion of an inherited disorder, particularly von Hippel–Lindau syndrome (see Chapter 21.12; cystic and solid lesions, some malignant) or tuberous sclerosis (see Chapter 21.12; benign lesions), both having autosomal dominant inheritance.

Lymphoma and leu- kaemia may occasionally invade the renal substance on a sufficient scale to cause renal impairment, but it is rare for other tumours to do so. A rare and aggressive renal medullary tumour has been described in young patients with sickle cell trait or disease. These are easily confused with tumours of the collecting system and carry a poor prognosis. The collecting system and lower urinary tract may be affected by transitional cell tumours or by malignancies that may invade the tract bilaterally or below the bladder. Transitional cell tumours af- fecting the bladder are common, and sometimes cause renal mani- festations if extensive. Lesions in the ureters and collecting system are less common. They occur multifocally in association with anal- gesic nephropathy and two conditions caused by aristolochic acid- ('Chinese herb') nephropathy and Balkan endemic nephropathy (see Chapter 21.9.2). Metabolic effects of malignancies on the kidney Hypercalcaemia is a feature of many malignancies, both with and without metastasis. Its renal effects are discussed in Chapter 21.14. Hypokalaemia may be a consequence of acute leukaemias or rectal tumours, and may occasionally be severe enough to cause renal dys- function (see Chapter 21.2.2). Severe hyperuricaemia (>900 μmol/litre) is characteristically as- sociated with massive cell death occurring following chemotherapy of haematological or solid tumours (tumour lysis syndrome), when it is usually accompanied by marked hyperphosphataemia and often by hypocalcaemia. High serum lactate dehydrogenase levels may also be diagnostically useful. Similar gross hyperuricaemia may be seen following radiotherapy of radiosensitive tumours, or may occur without therapy in malignancies with a very high rate of cell turn- over, particularly acute lymphocytic or acute myeloid leukaemia, or poorly differentiated solid tumours. Uric acid levels this high can lead to precipitation within renal tubules and acute kidney injury. Prevention and treatment of tumour lysis syndrome is discussed in Chapter 21.10.5. Table 21.10.9.1 How malignant disease affects the kidney and urinary tract Mode of involvement Examples Direct Tumours of the renal substance Lymphoma, leukaemia deposits Remote metastases from solid tumours Tumours of the urinary tract, prostate gland, etc. Local invasion (cervix, colon) Metabolic and remote effects Hypercalcaemia Hypokalaemia Hyperuricaemia Thrombotic microangiopathy (tumour-associated thrombotic thrombocytopenic purpura) Deposition of tumour products Myeloma kidney (precipitation in tubules) Immunoglobulin deposition diseases Immune reaction Minimal- change disease (particularly with lymphomas) Membranous nephropathy (particularly with solid tumours) Rapidly progressive glomerulonephritis and small-vessel vasculitis Effect of treatment Tumour lysis syndrome Direct toxicity of drugs Idiosyncratic (e.g. immune) response

 Remote effects of malignant tumours on the kidney Thrombotic microangiopathy Thrombotic microangiopathy occurring in association with ma- lignant disease (also known as malignancy-associated thrombotic thrombocytopenic purpura; see Chapters 22.7.3 and 22.7.5) is often attributed to chemotherapy. It is particularly associated with certain agents (e.g. bleomycin, mitomycin), although isolated reports im- plicate others. However, in some instances the classic presentation with thrombocytopenia, microangiopathic haemolytic anaemia, and renal failure occurs in association with primary tumours. This has been particularly reported for malignancies of the stomach, pan- creas, and prostate. The syndrome is occasionally the presenting sign of malignancy but often occurs in a patient known to have a tumour. In the absence of specific evidence, tumour-related thrombotic microangiopathy is usually treated in the same way as throm- botic microangiopathy of other types, by plasma exchange for fresh frozen plasma. If the tumour itself is responsive to treatment, microangiopathy generally subsides too. Renal function may be re- coverable if the process is halted rapidly, an outcome that is most likely in prostatic carcinoma. Deposition of tumour products

The protean effects of monoclonal overproduction of immuno- globulins, or their component parts, are considered elsewhere (see Chapter 21.10.5). The tubulotoxic effects of freely filtered im- munoglobulin light chains may be amplified by hypercalcaemia in myeloma, or by concurrent administration of other nephrotoxins, notably intravenous radiological contrast media or possibly loop diuretics. AL amyloidosis (see Chapters 12.12.3 and 21.10.5) is an- other possible consequence of monoclonal proliferation of B cells, devastating enough on its own, but it may be associated with mye- loma or progress to overt myeloma. A variety of other renal con- sequences may occur in B-cell disorders with overproduction of immunoglobulin fragments, notably the light-chain (and rarer heavy-chain) deposition disorders. Immune reactions Malignant diseases are common, hence on occasions cancer will be associated with nephropathies by chance. There are many case re- ports in the literature, but some associations have been reported Causes of AKI in a patient with Malignancies Prerenal Causes • NSAIDS • Contrast • Sepsis • Hypotension • Diarrhea • N/V Renal Vein Thrombosis Renal Arterial Occlusion Artery Stenosis • Lymphadenopathy • Blood Clots • Tumor infiltration & Encasement, Fibrosis • Capillary Leak Syndrome lgM Thrombi, (Waldenstrom's Cryoglobulinaemia), Light Chain Deposition Disease Amyloidosis Drug Crystals ATI from Tubulotoxins Cast Nephrophathy Infiltration in plasma cell leukaemia or lymphoma Nephron Artery Vein Kidney Ureter lntrarenal Causes Bladder Urethra Post-renal Causes Fig. 21.10.9.1 Summary of causes of acute kidney injury (AKI) in patients with cancer. ATI, acute tubular injury; NSAIDs, nonsteroidal anti- inflammatory drugs; N/V, nausea and vomiting. Reproduced with permission from Moeckel GW, Manjunath V, and Perazella MA. Acute kidney injury in the cancer patient. In: Turner N, Lameire N, Goldsmith DJ, et al. Oxford Textbook of Clinical Nephrology. 4th ed. Oxford: Oxford University Press (2015).

21.10.9 Malignancy-associated renal disease 5043 consistently and are beyond doubt. The best-supported linkages between malignancies and intrinsic renal diseases are for minimal- change disease and membranous nephropathy, glomerular condi- tions that are (membranous) or are believed to be (minimal-change) immunologically mediated. There is also a frequently reported asso- ciation of malignancy with various types of vasculitis, particularly small-vessel vasculitis, which—as with glomerulonephritis—is usually believed to be immunologically mediated, both because of the typical contexts in which it occurs and because of its usual response to immunosuppressive agents. By contrast, there is little evidence for association of malignancies with primary interstitial renal diseases. Some malignancies are particularly likely to be associated with renal disease. Chronic lymphocytic leukaemia and similar low- grade B-cell tumours are associated with a variety of types of glomerulopathy. Thymomas have frequently been associated with glomerular lesions, usually causing nephrotic syndrome with various histological patterns reported. Minimal-change nephrotic syndrome Lymphomas, usually Hodgkin’s disease, are rarely associated with minimal-change nephropathy. The renal lesion is typical in patho- logical characteristics, and usually also in response to cortico- steroid treatment. In exceptional cases, this is the presenting sign of the lymphoma, and it may also herald relapse. More so than with other renal lesions that are putatively associated with ma- lignancy, there is often a close temporal relationship between the occurrence of nephrotic syndrome and the presentation of the tu- mour. However, there is no way of proving the association in an individual patient, or of suspecting an underlying lymphoma in patients who present with nephrotic syndrome without systemic symptoms. As the association is very rare in comparison to the number of young patients with minimal-change disease, screening other than by clinical examination and simple investigations is not justified. Less commonly, minimal-change disease has been associated with solid tumours, and

particularly with malignant and benign thymomas. Membranous nephropathy Membranous nephropathy is caused by antibody (autoanti- body) formation to any of several molecules on the surface of the podocyte. It has often been associated with malignancies, but mem- branous nephropathy is not rare and occurs in older patients who are at relatively high risk of malignancy simply on account of their age. Series have shown rates of malignancy from 5 to 11%, although the risk is greater in older patients. However, variation in reporting practice makes published figures difficult to interpret, for example, if tumours that are recognized long after the renal diagnosis are in- cluded. Most reported tumours are of solid organs, including al- most all types, but haematological malignancies are also implicated. Very often the disease is advanced and obvious when nephrotic syndrome or heavy proteinuria is recognized. In some cases, the nephrotic syndrome or proteinuria lessens after effective treatment of the malignancy. The use of alkylating agents or corticosteroids as treatment for the membranous nephropathy is not recommended in this setting, unless this would be appropriate for treatment of the malignancy itself. There is controversy about the value of screening for malig- nancy in patients presenting with membranous nephropathy when malignancy is not apparent from initial investigations. Aside from routine haematological and biochemical investi- gations, chest radiography, and renal ultrasonography that are needed in all cases of nephrotic syndrome, in older patients it is appropriate to perform careful breast and rectal examination, faecal occult blood screening, and possibly mammography and sigmoidoscopy or colonoscopy. However, in clinical practice, the number of treatable and otherwise subclinical tumours un- covered in this way is low. Systemic vasculitis Focal necrotizing and crescentic nephritis, with or without evi- dence of small-vessel vasculitis affecting other organs, may occur in association with malignancy. Some cases may be chance asso- ciations of malignancy with typical small-vessel vasculitis that is not uncommon in older people, but there are sufficient reports of unusual associations to strongly suggest that there is sometimes a causal relationship. As well as true vasculitis, cancer-related thrombotic microangiopathy and thrombotic events compli- cating disseminated intravascular coagulation in association with cancer may resemble systemic vasculitis and lead to diagnostic confusion. The most common type of vasculitis to be associated with ma- lignancy is small-vessel cutaneous vasculitis. In other cases, bowel and other organs including the kidney have been involved by a small- to medium-vessel systemic vasculitis, which is usually antineutrophil cytoplasmic antibody (ANCA) negative. However, more typical ANCA-associated vasculitis has also been associated with malignancy, and there may be a particular relationship between granulomatosis with polyangiitis (formerly known as Wegener’s granulomatosis) and renal cell carcinoma. Usually the kidney is not involved in cancer-associated systemic vasculitis, but when it is, the appearances are indistinguishable from those of small-vessel vascu- litis of other aetiologies. Immune deposits in glomeruli are not usual (pauci-immune). Atrial myomas have been associated with lesions of larger and smaller vessels, and it appears that embolization is not always the explanation for this. Effects of treatment for malignancy These include the tumour lysis syndrome (discussed earlier and in Chapter 21.10.5), as well as idiosyncratic or predictable reactions to therapeutic agents. On occasions, minimal-change disease or other proteinuria- causing lesions have been associated with treatment with inter- ferons and with drugs that target vascular endothelial growth factor (VEGF) or its signalling. Anti-VEGF therapy may also cause thrombotic microangiopathy. The bisphosphonate pamidronate has caused proteinuria and focal segmental glomerulosclerosis, usually when given at high doses in myeloma. Cisplatin may cause tubular damage, predominantly to proximal tubules, and is characteristically associated with features of a renal Fanconi syndrome (see Chapter 21.16), although there can also be significant loss of glomerular filtration rate when severe. Ifosfamide,

section 21 Disorders of the kidney and urinary tract 5044 but not cyclophosphamide, is also prone to cause permanent tubular damage. High-dose methotrexate and pemetrexed may cause tubular damage. Radiation nephropathy develops slowly and is termed acute if it occurs within 6 months of exposure. Hypertension is usually a prominent feature, and there may be accompanying thrombotic microangiopathy. Chronic radiation nephropathy appears from 1 to 20 years after exposure and typically presents indolently with chronic kidney disease, with imaging revealing small kidneys. FURTHER READING Bacchetta J, et al. (2008). Paraneoplastic glomerular diseases and ma- lignancies. Crit Rev Oncol Haematol, 70, 39–58. Biava CG, et al. (1984). Crescentic glomerulonephritis associated with nonrenal malignancies. Am J Nephrol, 4, 208–14. Dabbs DJ, et al. (1986). Glomerular lesions in lymphomas and leuke- mias. Am J Med, 80, 63–70. Goel A, et al. Renal medullary carcinoma. Radiopaedia. http:// radiopaedia.org/articles/renal-medullary-carcinoma Gordon LI, et al. (1999). Thrombotic microangiopathy manifesting as thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in the cancer patient. Semin Thromb Hemost, 25, 217–21. Gupta R, Billis A, Shah RB (2012). Carcinoma of the collecting ducts of Bellini and renal medullary carcinoma: clinicopathologic analysis of 52 cases of rare aggressive subtypes of renal cell car- cinoma with a focus on their interrelationship. Am J Surg Pathol, 36, 1265–78. Gurevich F, Perazella MA (2009). Renal effects of anti-angiogenesis therapy: update for the internist. Am J Med, 122, 322–8. Izzedine H, et al. (2006). Drug-induced glomerulopathies. Exp Opin Drug Saf, 5, 95–106. Izzedine H, et al. (2010). VEGF signalling inhibition-induced protein-uria: mechanisms, significance and management. Eur J Cancer, 46, 439–48. Kurzrock R, Cohen PR, Markowitz A (1994). Clinical manifestations of vasculitis in patients with solid tumors. A case report and review of the literature. Arch Intern Med, 154, 334–40. Maher ER (2011). Genetics of familial renal cancers. Nephron Exp Nephrol, 118, e21–6. Markowitz GS, et al. (2001). Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. J Am Soc Nephrol, 12, 1164–72. Markowitz GS, Bomback AS, Perazella MA (2015). Drug-induced glomerular disease: direct cellular injury. Clin J Am Soc Nephrol, 10, 1291–9. O'Callaghan CA, et al. (2002). Characteristics and outcome of membranous nephropathy in older patients. Int Urol Nephrol, 33, 157–65. Pabla N, Dong Z (2008). Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. Kidney Int, 73, 994–1007. Ronco PM (1999). Paraneoplastic glomerulopathies: new insights into an old entity. Kidney Int, 56, 355–77. Turner AN, et al. (eds) (2015). Oxford textbook of clinical nephrology, 4th edition. Oxford University Press, Oxford. Watts RA, Scott DG, Mukhtyar C (2015). Secondary vasculitis. In: Vasculitis in clinical practice, pp. 173–84. Springer International Publishing AG, Cham. 21.10.10 Atherosclerotic renovascular disease Philip A. Kalra and Diana Vassallo ESSENTIALS Atherosclerotic renovascular disease (ARVD) refers to atheromatous narrowing of one or both renal arteries and frequently coexists with atherosclerotic disease in other vascular beds. Patients with this con- dition are at high risk of adverse cardiovascular events, with mortality around 8% per year. Many patients with ARVD have chronic kidney disease, but only a minority progress to endstage kidney disease, suggesting that pre-existing hypertensive and/or ischaemic renal parenchymal injury is the usual cause of renal dysfunction. Many patients with ARVD are asymptomatic, but there can be important complications such as uncontrolled hypertension, rapid decline in kidney function, and recurrent acute heart failure (flash pulmonary oedema). Management—patients with ARVD should receive medical vas- cular protective therapy just like other patients with atheromatous disease. This involves antiplatelet agents such as aspirin, statins, antihypertensive agents (angiotensin-converting enzyme inhibi- tors or angiotensin receptor blockers are the drugs of choice), opti- mization of glycaemic control in diabetic patients, and advice/help to stop smoking. On the basis of randomized controlled trial data, the majority of

patients should not be offered revascularization by angioplasty/stenting for the purpose of improving blood pressure control or stabilizing/improving renal function. However, there is evidence that a subgroup of patients with specific complications of ARVD (as previously mentioned) may benefit from revascularization. Introduction Atheromatous disease is common, indeed almost universal in elderly individuals, and it is a multiorgan disease process. Atherosclerotic renovascular disease (ARVD) refers to atheromatous narrowing or occlusion of one or both renal arteries and as expected, occurs more frequently with increasing age and in the presence of cardiovascular risk factors such as diabetes, smoking, and hypertension. Although ARVD is very often asymptomatic and usually discovered inciden- tally during investigation for extrarenal atherosclerotic disease, haemodynamically significant stenosis in certain patients can lead to important complications such as uncontrolled hypertension, pro- gressive decline in kidney function, and recurrent episodes of acute heart failure (flash pulmonary oedema). The heterogeneous nature of ARVD poses a significant diag- nostic and management dilemma to the physician. Despite signifi- cant progress in imaging techniques, accurate determination of the haemodynamic significance of a stenosis remains difficult. In addition, percutaneous revascularization carries a risk of complica- tions and does not guarantee improved outcomes. This is probably due to irreversible renal parenchymal damage in the poststenotic kidney, a product of both local (e.g. oxidative stress) and systemic

 (e.g. longstanding hypertension, diabetes) insults. This would ex- plain the neutral results of recent large prospective trials in ARVD, which have shown that revascularization does not confer any added benefit to optimal medical therapy in unselected populations. However, there is evidence that subgroups of patients with a ‘high- risk’ phenotype, for example, patients with recurrent flash pul- monary oedema, or refractory hypertension in conjunction with rapidly declining renal function, do benefit from revascularization. Identifying these patients in a timely manner remains a consider- able challenge. The issue of investigation and treatment of renal artery stenosis (RAS) in the context of the patient presenting with hypertension is discussed in Chapter 16.17.3. This brief chapter focuses more on pa- tients with impairment of renal excretory function (chronic kidney disease) with reduced (and falling) estimated glomerular filtration rate (eGFR) in association with ARVD. The underlying aetiology, genetics, pathogenesis, and histopath- ology of the major macrovascular RAS lesions in ARVD are broadly as for atherosclerotic disease in general (see Chapter 16.13.1). However, as already mentioned, histopathological changes in the kidneys of patients with chronic kidney disease associated with ARVD can include hypertensive and ischaemic injury, as well as atheroembolic disease. The latter is a recognized cause of acute kidney injury occurring after revascularization. Epidemiology It is difficult to state the true incidence and prevalence of ARVD because of variability in both the definition and in the enthusiasm with which the diagnosis is pursued. There is no uniform agreement about the precise degree of RAS which constitutes a haemodynam- ically significant lesion. However, in the context of the patient with gradually failing renal function, in which the causal mechanism might be ‘ischaemic renovascular disease’ (ischaemic nephropathy), many consider that the presence of significant high-grade RAS (>70% narrowing of both renal arteries, or of the artery to a single functioning kidney) is necessary to make the diagnosis. Most ARVD epidemiological studies have been performed in populations with known atherosclerosis or cardiovascular risk factors, hence leading to selection bias. A study of administra- tive claims data from the United States Medicare population over 67 years of age gave an incidence of 3.7/1000 patient years. The overall prevalence in such patients is around 0.5%. Another study in which healthy individuals over 65 years of age living in the United States of America were screened for

ARVD by means of a dop- pler ultrasound scan reported an incidence of 6.8%. However, the prevalence of ARVD in populations with significant comorbidities is much higher—unsuspected ARVD has been found in around 25% of patients with peripheral vascular disease and in up to 50% of patients with congestive heart failure. In various studies RAS has been demonstrated in 5 to 22% of patients with endstage renal dis- ease aged over 50 years, but the presence of ARVD here does not al- ways imply causality of the renal dysfunction. Conversely, patients with ARVD usually have evidence of other macrovascular disease such as coronary (67%), peripheral arterial (56%), and cerebrovas- cular (37%) atherosclerotic disease. Some atherosclerotic RAS lesions become worse with time, but this is not inevitable, especially since the advent of modern, multitargeted medical management of atherosclerosis, which in- cludes statins and tight risk factor control. Serial imaging studies performed in the pre-statin era reported a rate of progression to occlusion of up to about 40% over 12 months' follow-up, leading to loss of renal function and renal atrophy. However, nowadays, progression to total occlusion occurs much less commonly, and later studies have reported a rate of occlusion of 3% over 3 years. Clinical features The diagnosis of ARVD should be suspected in any patient with other manifestations of atherosclerosis who presents with stable chronic kidney disease or progressive impairment of renal func- tion, especially in the presence of hypertension that is particularly severe or difficult to control. Other clinical pointers are the pres- ence of abdominal or iliofemoral bruits, significant deterioration in renal function after initiation of treatment with an angiotensin- converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), and asymmetry of renal size on imaging (>1.5 cm difference in length of the two kidneys). Flash pulmonary oedema is a well-described and 'classic' manifestation of ARVD, but pul- monary oedema in a patient with ARVD is more usually attrib- utable to concurrent ischaemic cardiac disease. ARVD is now increasingly recognized in association with congestive cardiac failure. Clinical investigations ARVD can only be confirmed by some form of imaging and the main techniques used include duplex Doppler ultrasonography (very operator dependent) (Figs. 21.10.10.1 and 21.10.10.2), mag- netic resonance angiography (either contrast free or with gado- linium, although the latter is contraindicated in patients with an eGFR <30 ml/min per 1.73 m2; see Chapter 21.4), CT angiography (which requires administration of nephrotoxic contrast media) (Fig. 21.10.10.2), and digital subtraction angiography (which requires ar- terial puncture/instrumentation and administration of nephrotoxic contrast media). The investigative approach will be determined by local availability and expertise. Note that, with the exception of high-quality arterial Doppler studies, none of the above-mentioned tests assess functional significance of the RAS lesion, which remains a major deficiency in the investigation and management of patients with ARVD. The urine may contain some protein (albumin:creatinine ratio uncommonly >50 mg/mmol), but is bland, without red cells or casts. Management All patients with ARVD should receive interventions appropriate for any patient with known atherosclerotic disease, including encouragement of and assistance with smoking cessation, aspirin

 (or other antiplatelet agents), statin therapy, blood pressure control, and in patients with diabetes, optimization of glycaemic control. Early studies discouraged the use of ACE inhibitors or ARBs in patients with RAS as they were thought to decrease perfusion pres- sure across a stenosis and exacerbate renal injury, but subsequent studies confirmed that renin–angiotensin blockade can both miti- gate the intrarenal parenchymal injury that leads to chronic kidney disease in ARVD and improve overall survival by optimizing cardiac status. In view of this, ACE inhibitors and ARBs are now considered the antihypertensive agents of choice in patients with ARVD. Nonetheless, a minority of patients with

bilateral RAS or severe RAS affecting a solitary functioning kidney are at risk of acute kidney injury with such therapy, hence close monitoring of kidney func- tion after initiation of an ACE inhibitor or ARB is essential. Blood pressure and renal chemistry should be checked within 2 weeks of starting renin–angiotensin blockade in any patient, and especially in those with RAS. Renal function should then be rechecked on a 6-monthly basis once the patient is receiving a stable maintenance dose, and more frequent monitoring may be required in patients who are on concurrent diuretic therapy or aldosterone antagonists. If, following initiation of an ACE inhibitor or ARB, serum creatinine concentration increases by more than 30% or eGFR declines by more than 25%, and there is no other apparent precipitating cause of acute kidney injury such as dehydration or concurrent nephro- toxic medication (e.g. nonsteroidal anti-inflammatory agents), the dose of the ACE inhibitor or ARB may need to be reduced to a previously tolerated level or stopped altogether. Hypotension may cause an acute decline in GFR due to impaired autoregulation in patients with chronic kidney disease or in those with critical RAS receiving an ACE inhibitor or ARB. In the event of an intercurrent illness which can cause hypotension, such as diarrhoea, vomiting, or sepsis, it should be recommended that the ACE inhibitor or ARB are temporarily stopped until the patient has recovered. Such advice is now part of ‘Sick Day rules’ programmes for prevention of acute kidney injury. A key management question concerns whether renal revasculari zation with renal artery angioplasty/stenting is warranted. While there is no doubt that such interventional procedures can produce ‘anatomical cure’ of RAS (Fig. 21.10.10.3), there is a small chance (approximately 3%) of major debilitating complications including groin haematoma, acute kidney injury, cholesterol embolization, arterial dissection, and renal infarction. Fig 21.10.10.1 Normal right renal artery as assessed by colour Doppler ultrasound. Spectral analysis (bottom of image) shows low resistance waveform in the artery. From https://www.med-ed.virginia.edu/courses/rad/gu/anatomy/kidneys.html. (a) (b) Fig 21.10.10.2 Panel (a) shows a CT angiogram with the red arrow indicating significant stenosis in the right renal artery. Panel (b) shows the colour Doppler ultrasound appearance compatible with the angiographic findings. An elevated peak systolic velocity of 246.6 cm/s is noted at the area of stenosis. (a) From http://www.radblazer.com/renal-artery-stenosis-angiogram/. (b) From https://iame.com/online/duplex_and_color_doppler_of_the_kidney/content.php.

21.10.10 Atherosclerotic renovascular disease 5047 A number of studies have been carried out over the past two decades to determine whether anatomical improvement trans- lates into clinically useful outcomes for patients, and to assess how revascularization compares with modern multitargeted medical management. Results from small randomized controlled trials showed no clear evidence of benefit for revascularization over con- servative medical management. The largest and most recent ran- domized controlled trials, the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) and Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) studies, provide the most robust data regarding the role of revascularization in the management of patients with ARVD. The United Kingdom-based ASTRAL trial randomized 806 patients with ARVD to either medical therapy alone or medical therapy with revascularization. The primary endpoint was change in renal function from baseline and after a median follow-up of 34 months. Results showed that revascularization had no impact on decline in renal function or on blood pressure control, incidence of cardiovascular events, or mortality (secondary endpoints), and there was a significant complication rate of 7% associated with the procedure. The CORAL study was based in the United States of America (although around 50% of patients were from the rest of the world), and is the largest study in ARVD to date; 947 patients were random- ized to stenting and best medical

therapy or best medical therapy alone. The primary endpoint was a composite of major cardiovascular events, progressive deterioration in renal function, and death from cardiovascular or renal causes. Again, after a median follow-up of 43 months, revascularization did not confer any clinical benefit over medical therapy on its own. However, a major criticism of these ARVD trials is the fact that these results may not be entirely generalizable as patients with 'high- risk' features (e.g. uncontrolled hypertension, rapidly deteriorating renal function, or unstable cardiac status) were specifically excluded. A recent single-centre retrospective study looked at 237 patients with at least 50% RAS and one or more 'high-risk' features. Around one-quarter (24%) of these patients underwent revascularization and their outcomes were compared with those of patients who were treated exclusively medically. Revascularization led to improved clinical outcomes in patients with either flash pulmonary oedema or a combination of rapidly declining kidney function and uncontrolled hypertension. Our recommendation is that there is no benefit in screening asymptomatic patients with chronic kidney disease and/or hyper- tension for ARVD, and that most patients found to have ARVD should generally not be referred for revascularization for the purpose of improving blood pressure control or stabilizing/ improving renal function. There is, however, some evidence that revascularization may play a role in the management of an im- portant subset of patients with certain 'high-risk' features who have not been well-represented in clinical trials. These include patients with severe RAS and with otherwise unexplained rapid decline in renal function, those with recurrent episodes of flash pulmonary oedema (not explained by cardiac disease), and per- haps those with severe hypertension not adequately controlled by multiple drug treatments (or in whom reduction in arterial pres- sure leads to significant decline in eGFR). Another subgroup who (a) (b) (c) Fig 21.10.10.3 An intra-arterial digital subtraction angiography series showing left renal angioplasty and stent placement. (a) Flush aortogram showing severe (>95%) left renal artery stenosis (arrow); the more distal circulation beyond the stenosis is just visible. (b) The angioplasty catheter (arrow) has traversed the renal artery stenosis. (c) A stent has been deployed (arrow). Courtesy of Professor J. Moss, Gartnavel Hospital, Glasgow.

 could justifiably be treated with revascularization are those who require ACE inhibitors or ARBs because of concomitant heart disease and/or renal parenchymal injury, but show intolerance of these drugs as manifest by acute kidney injury. Prognosis Patients with ARVD are at a higher risk of cardiovascular events and death than the general population due to their significant athero- sclerotic burden. However, renal function tends to remain stable and only rarely do patients with ARVD require renal replacement therapy due to ARVD progression. Indeed, in the Medicare popu- lation in the United States of America, the risk of mortality during follow-up was almost six times that of requiring renal replacement therapy. Recent trials in ARVD have shed light on the heterogeneous nature of this condition and how prognosis may be quite vari- able. This is illustrated by the different baseline characteristics of patients enrolled into the ASTRAL and CORAL trials and their slightly divergent outcomes; the average eGFR for ASTRAL was 40 ml/min per 1.73 m2 whereas that for CORAL was higher, approxi- mately 58 ml/min per 1.73 m2. As a result, mortality was around 8% per year for ASTRAL, compared to around 4% per year for CORAL, whereas the incidence of endstage kidney disease was 2% per year for ASTRAL and 0.5% per year for CORAL. Nonetheless, the results of both of these trials highlight the steady improve- ment in the prognosis of ARVD that has occurred over the past few decades, a testament to the reno- and cardioprotective effects of modern medical therapy. Future developments Timely identification of individuals who may gain benefit from revascularization remains a very important challenge to clinicians, and recent progress in imaging

and diagnostic technology may help address this issue. Novel functional magnetic resonance imaging (MRI) techniques such as blood oxygen level-dependent (BOLD)- MRI may estimate the degree of intrarenal hypoxia and thus help identify critically ischaemic kidneys. MRI has also been used to measure single-kidney GFR and other perfusion parameters that may correspond to the functional status of the kidney. Indeed, a high single-kidney GFR-to-parenchymal volume ratio has been shown to identify kidneys that may be salvaged by revascularization because they retain viable or 'hibernating parenchyma'. Progress in biomarker technology over the past decade has stimulated interest in the identification of serum or urine biomarkers, such as neutro- phil gelatinase-associated lipocalin (NGAL), tubular kidney injury molecule-1 (KIM-1), or brain natriuretic peptide (BNP), which can help predict outcomes post revascularization. However, these novel techniques have only been studied under experimental conditions and more research is required to determine whether they can be ap- plied to clinical practice. Increased understanding of the complex pathogenesis of renal parenchymal injury in ARVD has paved the way for novel thera- peutic strategies. Cell-based therapies have been proposed to counteract the inflammatory milieu and oxidative stress typically found in the poststenotic kidney. These might prevent irreversible loss of renal microvascular architecture and help improve clinical outcomes. FURTHER READING Bax L, et al. (2009). Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. Ann Intern Med, 150, 840–8. Cheung CM, et al. (2006). MR-derived renal morphology and renal function in patients with atherosclerotic renovascular disease. Kidney Int, 69, 715–22. Cooper CJ, et al. (2014). Stenting and medical therapy for atheroscler- otic renal-artery stenosis. N Engl J Med, 370, 13–22. Chrysochou C, et al. (2012). BOLD imaging: a potential predictive biomarker of renal functional outcome following revascularization in atheromatous renovascular disease. Nephrol Dial Transplant, 27, 1013–19. Eirin A, Textor SC, Lerman LO (2019). Novel therapeutic strategies for renovascular disease. Curr Opin Nephrol Hypertens, 28, 383–9. Herrmann SMS, Saad A, Textor SC (2014). Management of athero- sclerotic renovascular disease after Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL). Nephrol Dial Transplant, 30, 366–75. Kalra PA, et al. (2005). Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularization, and prognosis. Kidney Int, 68, 293–301. National Institute for Health and Care Excellence (2013). Acute kidney injury: prevention, detection and management. Clinical guideline [CG169]. National Institute for Health and Care Excellence, London. National Institute for Health and Care Excellence (2014). Chronic kidney disease: in adults: assessment and management. Clinical guide- line [CG182]. National Institute for Health and Care Excellence, London. Ritchie J, et al. (2014). High-risk clinical presentations in atheroscler- otic renovascular disease: prognosis and response to renal artery revascularization. Am J Kidney Dis, 63, 186–97. Saad A, et al. (2013). Stent revascularization restores cortical blood flow and reverses tissue hypoxia in atherosclerotic renal artery sten- osis but fails to reverse inflammatory pathways or glomerular filtra- tion rate. Circ Cardiovasc Interv, 6, 428–35. The ASTRAL Investigators (2009). Revascularisation versus medical therapy for renal-artery stenosis. N Engl J Med, 361, 1953–62.

ESSENTIALS Kidney diseases encountered in tropical areas are a mix of conditions that have a worldwide distribution and those that are secondary to factors unique to the tropics, for example, climatic conditions, infec- tious agents, nephrotoxic plants, envenomations, and chemical toxins. Cultural factors, illiteracy, superstitions, living conditions, level of access to health care, and nutritional status also affect the nature and course of disease. Knowledge of such conditions and issues is important for medical professionals in all parts of the globe, as ease of travel means that

individuals and practices are exported with increasing frequency. Glomerular diseases—there is a high prevalence of infection-related glomerulonephritis throughout the tropics, with the pattern of in- jury dependent upon the nature of the prevalent endemic infection in that region. Important infection-related glomerulopathies include quartan malarial, schistosomal, and filarial nephropathies. Once es- tablished, the course of disease is rarely modified by treatment of underlying infection. Acute kidney injury (AKI)—there is a higher prevalence of community-acquired AKI in the tropics than elsewhere. Medical causes predominate, with diarrhoeal diseases, intravascular haem- olysis due to glucose-6-phosphate dehydrogenase deficiency, inges- tion of toxic plants, snake bites, insect stings, and locally prevalent infections being responsible for most cases, although obstetric causes remain common in some tropical countries. Falciparum malaria and leptospirosis are the most important infectious aetiologies. Use of in- digenous herbs and chemicals by traditional healers (‘witch doctors’) are the most important toxic causes of AKI in sub-Saharan Africa. Chronic kidney disease (CKD)—although the contributions of dia- betes and hypertension are growing, many cases are secondary to glomerular diseases, likely infection related, or have CKD of undeter- mined aetiology. Many of the latter are agriculture or farm workers presenting with chronic tubulointerstitial nephritis of unknown cause. Introduction Approximately 40% of the world’s population live in the tropics, geographically defined as the area between the latitudes 23° north to 23° south. Kidney diseases in tropical areas are a variable mix of globally encountered conditions and those specific to the geopolit- ical characteristics of the region. Tropical ecobiology strongly influences the pattern and presen- tation of kidney diseases encountered. Tropics are characterized by high ambient temperature; some regions receive heavy rains, while other areas are arid, with little precipitation. Extreme heat and hu- midity can lead to unrecognized fluid losses, especially among those engaged in manual labour. Studies have demonstrated that people can lose up to 5 kg of weight during the course of a day and show features of subclinical rhabdomyolysis, both of which can lead to kidney injury. Rains force leaching of minerals and organic compounds from the fragile tropical soil into flowing water, which can leading to waterlogging and contamination of fields with potentially toxic metals. The combination of high temperatures, wet weather, and sal- inity support growth of a variety of flora and fauna, including poten- tially nephrotoxic plants, pathogenic microorganisms, and animals that can serve as disease vectors and intermediate hosts. The end re- sult is a high prevalence of waterborne and infectious diseases, many of which are associated with kidney injury. Rains cause a spike in the incidence of nephrotoxic snake bites, since flooding of snake bur- rows forces their inhabitants to come to the surface. Population migration over millennia has led to accumulation of certain genetic traits that increase kidney disease risk in the tropics. These include glucose-6-phosphate dehydrogenase (G6PD) deficiency giving rise to intravascular haemolysis and pigment- induced acute kidney injury (AKI); progressive kidney disease in haemoglobinopathies such as sickle cell anaemia and thalassaemias; MYH9 and APOL1 alleles predisposing to HIV-associated kidney disease; and hypokalaemia, hypercalcaemia, hypocitraturia, and renal tubular acidosis due to inherited defects in tubular transport. Compared to countries in temperate regions, tropical countries are disadvantaged in socioeconomic terms. Except for two small countries (Singapore and Hong Kong), all tropical countries are classified in low- or middle-income categories. Poorly developed healthcare systems reduce access of large populations to medical services. Traditional health systems that rely on unproven and po- tentially harmful therapies flourish in the tropics, some of which are associated with practices that increase kidney disease risk. 21.11 Renal diseases in the tropics Vivekanand Jha

section 21 Disorders of the kidney and urinary tract 5050 Cultural factors, illiteracy, superstitions, poor living conditions, and nutritional status also affect the nature, presentation, and course of kidney disease. Delayed diagnosis leads to extreme presentations that have been (almost) eliminated in the developed world. For ex- ample, it is not uncommon for children with distal renal tubular acidosis to present with marked skeletal deformities and severe growth retardation, or those with posterior urethral valves to go un- diagnosed until they are several years old. Acute renal cortical ne- crosis following septic abortion and placental abruption continues to be seen regularly. Malnutrition exaggerates the impact of kidney disease; a lower degree of protein loss leads to more severe periph- eral oedema and serous effusions. Delayed and suboptimal treat- ment leads to loss of opportunities to implement preventive and/ or curative therapies, thereby increasing morbidity and mortality. Economic considerations also prevent the implementation of more refined technological solutions. For example, continuous renal replacement therapy is eschewed in favour of cheaper and less com- plex peritoneal dialysis. In an era of easy transcontinental movement of people, organ- isms, and materials, all physicians and nephrologists need, more than ever before, to be aware of tropical renal diseases. People who have migrated from the tropics may continue to engage in habits that predispose to kidney disease, even in their new location. Slowly pro- gressive diseases due to past exposures in the tropics may produce delayed clinical manifestations. This chapter highlights the important differences between dif- ferent syndromes of kidney disease in the tropics and the rest of the world, and discusses some specific renal diseases unique to the trop- ical regions. Types of renal disease Glomerular diseases The overall prevalence of glomerulonephritis is reported to be higher in tropical countries than in temperate regions. Surveys from hos- pitals in sub-Saharan Africa show that nephrotic syndrome accounts for 0.2 to 4% of all admissions. Primary glomerular diseases account for the majority, but secondary causes are responsible in 40 to 55% of patients in Zimbabwe and Jamaica. There is variation in the epidemiology, aetiology, clinical presen- tation, and natural history of glomerulonephritis between different tropical countries (Figs. 21.11.1 and 21.11.2). In general, there is a high prevalence of infection-related glomerulonephritis throughout the tropics, with the pattern of injury dependent upon the nature of the prevalent endemic infection in that region. Minimal-change disease is as frequent in Asia and North Africa as in the developed world, but is less common in the rest of Africa. In a study from South Africa, minimal-change disease was respon- sible for nephrotic syndrome in 75% of children of Indian ancestry, whereas only 13.5% of black children showed this lesion. A high frequency of proliferative glomerulopathies and steroid resistance is described in paediatric patients from the Democratic Republic of Congo, Zimbabwe, Malawi, Nigeria, Kenya, and Uganda. Membranous nephropathy is seen with a high frequency among children with nephrotic syndrome in countries with a high hepatitis B virus (HBV) carrier rate, and in some areas HBV-related disease accounts for up to 15% of all membranous nephropathy cases. By contrast, mesangial proliferative forms with IgA deposits seem to be more common in adults with HBV infection. A strong (and likely causal) association has been described between chronic hepatitis C virus (HCV) infection and several chronic glomerular diseases. An autopsy study revealed glomerular lesions in 55% of HCV-infected individuals, including mesangial proliferative glomerulonephritis (17.6%), membranoproliferative glomerulonephritis (11.2%), and membranous nephropathy (2.7%). Recent population-based studies have shown a link between the prevalence of HCV infection and proteinuria. The introduction of new treatments for HCV is likely to reduce the prevalence of HCV-related glomerulonephritis. Postinfectious glomerulonephritis continues to be encountered in high frequency throughout the tropics. In studies from north Africa and the Middle-East, about 15 to 20% of all paediatric biopsies show diffuse proliferative

glomerulonephritis, likely postinfectious. The prevalence of poststreptococcal glomerulonephritis in the Goajiro Jamaica Ghana Sudan South Africa Pakistan Papua New Guinea Singapore North India Europe 0% 20% 40% 60% 80% 100% Minimal change Diffuse proliferative Membranous Mesangiocapillary Mesangioproliferative FSGS Others Fig. 21.11.1 Prevalence of different types of glomerular lesions in adults with nephrotic syndrome in different parts of the world. FSGS, focal segmental glomerulosclerosis. United Kingdom South Africa (Blacks) Zimbabwe South India Nigeria North India South Africa (Indians) Papua New Guinea 0% 20% 40% 60% 80% 100% Minimal change Diffuse proliferative Membranous Mesangiocapillary Mesangioproliferative FSGS Others Fig. 21.11.2 Prevalence of different types of glomerular lesions in children with nephrotic syndrome in different parts of the world. FSGS, focal segmental glomerulosclerosis.

21.11 Renal diseases in the tropics 5051 Indian community of Venezuela was twice that seen in other parts of the Goajira state. Acute kidney injury Community-acquired AKI is the commonest nephrological emer- gency encountered in the tropics, and referral patterns to dialysis units suggest a higher prevalence of community-acquired AKI in the tropics than elsewhere. In a large referral hospital in North India, 1.5% of all hospital ad- missions were referred to the nephrology service for management of moderate to severe AKI. Medical causes predominate, with diar- rhoeal diseases, intravascular haemolysis due to G6PD deficiency, ingestion of toxic plants, snake bites, insect stings, and locally prevalent infections being responsible for most cases, although obstetric causes remain common in some tropical countries (Figs. 21.11.3 and 21.11.4). In a recent global study conducted by the International Society of Nephrology, AKI patients in low- and low–middle-income coun- tries of the tropics were younger than those from rest of the world, although the extent to which this is explained by ascertainment bias remains uncertain. In a study from India, the average age of patients dialysed for AKI was 34.3 years. Dehydration was the most common cause of AKI, followed by infections, pregnancy-related AKI, and animal envenomation. Fig. 21.11.3 Map showing areas with a high prevalence of community-acquired AKI. Areas with a high prevalence of malaria-associated AKI are shown in maroon, and with intermediate prevalence in yellow; orange indicates areas with a high prevalence of both leptospiral and malarial AKI; textured fill in countries of sub-Saharan Africa indicates a high prevalence of malarial and herbal remedy-induced AKI; green indicates AKI of other causes. 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% North India South India Sri Lanka Thailand Nigeria S Africa Ghana Argentina Medical Surgical Obstetric Fig. 21.11.4 Causes of AKI in different tropical countries. Modified from Chugh, Satprija and Jha, Oxford Textbook of Clinical Nephrology, Oxford University Press, Oxford 2005.

section 21 Disorders of the kidney and urinary tract 5052 In contrast to patients with hospital-acquired AKI seen in tem- perate countries, the kidney is the sole affected organ in more than 50% of cases at diagnosis. However, when tropical AKI is seen as part of an undifferentiated illness that includes AKI, liver failure, respiratory failure, neurological dysfunction, disseminated intra- vascular coagulation, and metabolic acidosis, then establishing the cause can be impossible in the absence of specialized facilities. Lack of resources forces a significant proportion of patients with AKI in tropical low-income countries to go untreated, but the pro- portion of those receiving treatment who recover is greater than in the developed world, reflecting the relatively young age and absence of any pre-existing disease in the affected individuals. Saving Young Lives, a collaborative project between the International Society of Nephrology, International Paediatric Nephrology Association, International Society for Peritoneal Dialysis, and Sustainable Kidney Care Foundation, is developing a sustainable programme to treat AKI using peritoneal dialysis in sev- eral countries

of sub-Saharan Africa and Southeast Asia. Chronic kidney disease There are several notable differences in the pattern of chronic kidney disease (CKD) in topical populations compared to those in temperate zones. Tropical patients with endstage renal disease are significantly younger. Although the contribution of diabetes and hypertension to the overall CKD burden in the tropics is growing, a significant proportion develop CKD secondary to glomerular diseases, likely infection related, or have CKD of undetermined aetiology. Many patients come to medical attention for the first time with advanced renal failure and few prior symptoms. Most often, these are individuals from poor socioeconomic background and are agri- culture or farm workers who work long hours in hot and humid environments. Investigations reveal minimal proteinuria, bland urinary sediment, and smooth contracted kidneys. Kidney biop- sies in a few cases have shown bland tubulointerstitial nephritis. ‘Mini-epidemics’ of such cases has been reported from several trop- ical regions in central America (Costa Rica, Guatemala, Nicaragua, El-Salvador, Mexico), north America (California), South and Southeast Asia (India, Sri Lanka, Thailand), Middle-East (Saudi Arabia, Qatar), and Africa (Egypt, Sudan) (Fig. 21.11.5). Dubbed variously CKD of uncertain aetiology (CKDu), chronic interstitial nephritis in agricultural communities (CINAC) and other terms (e.g. mesoamerican nephropathy), the aetiology of this condition has been a subject of intense speculation. The currently favoured postulations include recurrent heat stress with episodes of dehy- dration and/or rhabdomyolysis, and exposure to agrochemicals, particularly pesticides. Other hypotheses are heavy metals (con- taminating drinking water, rice and edible fish), fluoride, tropical infections, dietary peculiarities, consumption of herbal medicines, and abuse of over-the-counter medications. See Chapter 21.9.2 for further discussion. Obstructive nephropathy due to urolithiasis is common in Pakistan, Thailand, and parts of India known as ‘stone belts’. Kidney diseases specific to the tropics In addition to nephropathies that have a worldwide distribution, some renal lesions have been described solely in residents of trop- ical countries. These can be broadly grouped under infectious and toxic categories. Causal relationships are suggested by epidemio- logical studies, demonstration of a temporal relationship between the inciting event (infection, environmental insult, or toxin exposure) and the development of renal manifestations, and by resolution following treatment of the infection or withdrawal of the insult. Improved diagnostic techniques and appropriately designed experi- mental studies have provided concrete evidence of a cause-and-effect relationship in some instances. Examples include establishment of aristolochic acid as the cause of Balkan endemic nephropathy, and identification of specific infections (e.g. scrub typhus, dengue, and leptospirosis) as the cause of undifferentiated febrile syndromes with Fig. 21.11.5 Tropical countries from where hot spots of chronic kidney disease of undetermined aetiology have been reported (red: definite; yellow: probable).

 AKI. Confirmation has been obtained by the demonstration of either the organism or microbial antigens in the renal lesions, and elution of specific antibodies in the case of infections, and toxic compounds in the case of plant and animal toxins. In some cases, animal models have provided insight into the genesis of the lesions. Infectious causes of renal disease in the tropics Table 21.11.1 shows the various tropical infections that can cause kidney injury. Malarial renal diseases Malaria, caused by members of the protozoan Plasmodium genus, is endemic in the Indian subcontinent, Middle East, East Asia, sub-Saharan Africa, and Central America. Of the five species patho- genic to humans, renal lesions have been described following in- fections with Plasmodium falciparum, P. vivax, P. knowlesi, and P. malariae, but not after P. ovale. Glomerulonephritis is the chief complication of P. malariae infection, whereas the others primarily present with AKI. Malarial AKI Less than 1% of all patients

with P. falciparum and P. knowlesi infec- tion develop AKI, but the prevalence increases to 60% in those with severe infection. Nonimmune visitors to an endemic area are more likely to develop severe infection than local residents. Malarial AKI has been reported from the Indian subcontinent, Thailand, Malaysia, and Africa. In recent years, AKI has been encountered in association with P. vivax infection, in particular from the Indian subcontinent. Molecular methods have permitted identification of human infec- tion with P. knowlesi, earlier thought to be limited to macaques in Malaysia, Thailand, Vietnam, Myanmar, and Philippines. Clinical features The initial symptoms are nonspecific and consist of malaise, headache, fatigue, muscle aches, fever, and chills. Nausea, vomiting, and hypo- tension are frequent in nonimmune individuals. Encephalopathy, acute respiratory distress syndrome, and disseminated intravascular coagulation indicate severe infection. AKI is usually seen by the end of the first week and is nonoliguric in 50 to 75% of cases. Haemolytic anaemia and cholestatic jaundice are frequent accompaniments. The so-called blackwater fever has seen a resurgence among nonimmune European expatriates, probably due to the reintroduction of quinine and mefloquine into the treatment regimen. Individuals with G6PD deficiency can develop severe haemolysis. Renal failure lasts from a few days to several weeks, with an average of 2 weeks. Investigations show azotaemia, hyponatraemia, hyperkalaemia, and lactic acidosis. Diagnosis requires the demonstration of asexual forms of the parasite in peripheral blood smears stained with Giemsa stain or acridine orange. Morphological features of P. knowlesi infection resemble those of P. falciparum in the early and P. malariae in the late stages, and accurate identification requires the use of molecular techniques. Test kits for rapid diagnosis of malaria on finger-prick blood samples are commercially available. These depend upon immunochromatographic detection of malaria antigens such as histidine-rich protein 2 (PfHRP2), lactate dehydrogenase (pLDH) or aldolase (pAldo). Useful in the field, these tests are relatively in- sensitive at low levels of parasitaemia and for nonimmune popula- tions. Other problems include false positivity and cross-reactivity between Plasmodium species. Pathology Acute tubular necrosis, characterized by cloudy swelling and degen- eration of tubular cells and casts loaded with malarial pigment, is the most prominent finding. Tubular cells contain haemosiderin gran- ules. Varying degrees of interstitial oedema and mononuclear cell infiltrate are also seen. Pathogenesis Kidney injury is attributed to haemorheological changes induced by the parasite that lead to renal ischaemia. P. falciparum merozoites consume and degrade erythrocyte proteins and alter the red cell Table 21.11.1 Tropical infections associated with kidney injury Class Organism Nature of renal lesion Protozoal Plasmodium malariae Glomerulonephritis Plasmodium falciparum AKI, TMA Plasmodium vivax and knowlesi AKI Schistosoma mansoni Glomerulonephritis Wuchereria bancrofti Glomerulonephritis Loa loa Glomerulonephritis Onchocerca volvulus Glomerulonephritis Bacterial Mycobacterium leprae Glomerulonephritis, amyloidosis Mycobacterium tuberculosis Glomerulonephritis, interstitial nephritis, destructive inflammation, amyloidosis Salmonella typhi and paratyphi Glomerulonephritis Shigella dystenteriae AKI, TMA Brucella abortus AKI Burkholderia pseudomallei AKI Vibrio cholera and vulnificus AKI Orient tsutsugamushi AKI Campylobacter jejuni AKI Viral Dengue haemorrhagic fever Glomerulonephritis, AKI Hantaan virus AKI Rift valley fever AKI Yellow fever Glomerulonephritis, AKI Spotted fever AKI HIV Glomerulonephritis, AKI, TMA Hepatitis B and C Glomerulonephritis Rotavirus, Norwalk agent AKI Spirochete Leptospira icterohaemorrhagica AKI, AIN, CKD Fungus Zygomycetes spp. AKI, renal infarction AIN, acute interstitial nephritis; AKI, acute kidney injury; CKD, chronic kidney disease; TMA, thrombotic microangiopathy.

section 21 Disorders of the kidney and urinary tract 5054 membrane, making the erythrocytes more spherical and less de- formable. Cup-shaped, electron-dense structures that overlie accre- tions of histidine-rich P. falciparum erythrocyte membrane protein and extrude an adhesive protein of high molecular weight are ex- pressed on the erythrocyte membrane and mediate attachment to endothelial cells, causing a phenomenon called ‘cytoadherence’. Infected erythrocytes adhere to uninfected red cells, platelets, monocytes, and lymphocytes. P. falciparum can also activate the alternate complement pathway and intrinsic coagulation cascade. Increased production of endothelin-1, increased plasma viscosity secondary to an increase in plasma fibrinogen, and rhabdomyolysis also contribute to the AKI. Contributory factors include volume depletion secondary to capillary leak and haemolysis. Studies from Thailand indicate that prior infestation with helminths protects against malarial AKI. Management Severe falciparum malaria requires supportive care in combin- ation with specific antimalarial treatment (see Chapter 8.8.2). Combination therapies, including artemisinin derivatives, are the norm. Careful fluid management is needed in patients with pul- monary oedema. Prognosis The mortality of malarial AKI is 10 to 40%. Late referral, high para- sitaemia, multiorgan involvement, and infection in previously unimmunized subjects portend a poor prognosis. Malarial glomerulopathy Before 1980, nephrotic syndrome was encountered during periods of intense transmission of P. malariae infection among children in western Nigeria, Uganda, Kenya, Côte d’Ivoire, Sumatra, New Guinea, and Yemen, with plasmodium positivity in 40 to 75% of cases. The prevalence of such quartan malarial nephropathy (the term quartan is used because the fever tends to return at 3-day inter- vals) has shown a sharp decline with the eradication of malaria, and the entity does not find a mention in recent reports. Clinical features The nephrotic syndrome develops several weeks after the onset of fever. Nonvisible haematuria is noted in about one-third of cases. Hypertension develops along with decline in renal function. Hypoalbuminaemia is profound, with values commonly less than 1 g/dl. The serum cholesterol level tends to be normal or low, re- flecting low dietary intake. Serum creatinine is usually normal at presentation. Glomerulonephritis in other malaria infections is usually clin- ically silent, but nonselective proteinuria, nonvisible haematuria, and casts are noted in 20 to 50% of cases with falciparum malaria. Glomerular lesions are seen at autopsy in about 18% of cases who die with P. falciparum and P. knowlesi infections. Pathology and pathogenesis The morphological appearance of quartan malarial nephropathy is of a mesangiocapillary pattern. Demonstration of malarial antigen in the deposits and binding of specific antibody to circulating mal- arial antigens suggest an immunological basis for the condition. Experimental studies also support this hypothesis. Environmental factors such as malnutrition or coinfection with Epstein–Barr virus may be permissive. The liver may act as a source of continuous antigen supply. Mild endocapillary glomerulonephritis has been de- scribed in falciparum malaria. Management Once established, quartan malarial nephropathy follows an inex- orably progressive course, culminating in renal failure within 2 to 4 years. Antimalarials and steroids have proved ineffective in ar- resting progression of kidney disease. Remission has been reported occasionally with cyclophosphamide, but there is no improvement in survival. By contrast, glomerulonephritis associated with falcip- arum malaria resolves within a few weeks of eradication of infection. Renal disease in schistosomal infections Schistosomiasis is a chronic infection caused by trematodes (blood flukes) and affects over 300 million people in Asia, Africa, and South America. Of the seven species pathogenic to humans, the most prevalent are Schistosoma haematobium (Africa and the Middle East), S. mansoni (South America and Africa), and S. japonicum (China and the Far East). S. haematobium primarily involves the lower urinary tract, whereas S. mansoni involves the gastrointes- tinal tract and portal system, leading to hepatic fibrosis and portal hypertension.

Schistosomal glomerulopathy Glomerulonephritis has been described in association with hepatosplenic schistosomiasis produced by S. mansoni. Reports from autopsy series in Brazil during the 1960s were followed by clin- ical observations from endemic areas of Africa, Saudi Arabia, and Yemen. Proteinuria has been reported in 1 to 22% of patients in- fected with S. mansoni and 2 to 5% with S. haematobium infection. Subclinical glomerular lesions were found in about 40% of patients with hepatosplenic schistosomiasis. Clinical features Though described at all ages, glomerulonephritis is most frequent in young adults with overt hepatosplenic disease. Males are affected twice as frequently as females. Peripheral oedema and ascites are the hallmarks; hypertension is seen in 50% of cases, appearing late in the disease. Proteinuria is poorly selective and haematuria uncommon. Complement levels are usually low. Nonspecific antibody produc- tion is demonstrated by false-positive rheumatoid factor or the VDRL (Venereal Disease Research Laboratory) tests. It is important to exclude other causes of nephrotic syndrome before attributing the lesions to schistosomiasis. Diagnosis is confirmed by demonstrating viable eggs in the stool or egg-containing granulomas in rectal or liver biopsies. Pathology Five patterns of glomerular pathology have been described (Table 21.11.2). The class I lesion is the earliest and most frequent, and is the principal lesion in renal allografts with recurrent schistosomal nephropathy. Class II lesions are more frequent in patients with concomitant salmonella infection. The frequency of class III le- sions varies from 20% in asymptomatic patients to over 80% in those with overt renal disease. The class IV lesion, seen in 15 to 40% of cases, cannot be distinguished from idiopathic focal segmental

 glomerulosclerosis on the basis of light microscopy, but immuno- fluorescence reveals IgA deposition. Class III and IV lesions are seen in patients with fibrotic livers and associated with severe hypocomplementaemia. Class V prevalence varies from 15 to 40%, with a higher frequency in African patients. This form is not usually affected by hepatic fibrosis. Pathogenesis The glomerulopathy is caused by the immunological reaction to specific schistosomal antigens. Antigens have been demonstrated in the glomeruli of baboons infected with S. mansoni, and circu- lating immune complexes have been documented in experimental animals and humans with hepatosplenic disease. Circulating com- plexes localize in mesangial and subendothelial locations, whereas the extramembranous deposits form in situ. Portocaval shunting prevents hepatic processing of worm antigen and delivers it directly into the systemic circulation. IgM anti- bodies are seen in most patients with hepatosplenic schistosomiasis alone, but circulating mononuclear IgA-bearing cells and IgA anti- bodies predominate in those with glomerular involvement. An iso- tope switch from IgM- to IgA-producing B cells is believed to be responsible for this alteration. An aberrant Th2 cytokine response contributes to organ damage. Genetic factors are thought to play a role; polymorphisms in IL13 and STAT6 genes have been associated with disease severity. The immune reaction may be modified by con- comitant infection with salmonella, hepatitis viruses, staphylococci, and mycobacteria. Epidemiological studies have shown clearance of urinary abnormalities following therapy for salmonella alone, sug- gesting a permissive role of this infection. Management Treatment of schistosomal glomerulopathy is disappointing. Antischistosomal drugs (see Chapter 8.11.1) do not alter the clin- ical course, which is one of inexorable progression to renal failure. Steroids or cytotoxic agents are similarly ineffective. Salmonella in- fection should be looked for and treated in all patients. Schistosomiasis involving the lower urinary tract The adult S. hematobium worm resides and lays eggs in the perivesical venous plexus, where they get trapped in the urinary tract mucosa and incite granuloma formation. Clinical manifestations appear when they coalesce into larger granulomata or polyps that ulcerate

and bleed. Over time, fibrosis and calcification set in. The presenting feature is painful haematuria, and characteristic ova with terminal spikes may be seen on urinary examination. Later stages are characterized by symptoms related to reduced bladder volume, obstruction to urine flow at the level of bladder outlet or ureterovesical junction, vesicoureteric reflux, or urinary tract infec- tion. Plain radiology may reveal linear or irregular calcification in the bladder wall, ureter, or seminal vesicles (Fig. 21.11.6). Bladder cancer is a complication of chronic schistosomal cystitis, and develops two to three decades after the initial infection in about 5% of all infected individuals. In Egypt, schistosomal eggs are dem- onstrated in over 85% of resected bladder cancer specimens. Long-standing obstruction leads to progressive loss of kidney function; 7 to 20% of the endstage renal disease population in Egypt is secondary to lower tract schistosomiasis. Renal disease in filarial infection Filarial worms are nematodes transmitted to humans through arthropod bites. Clinical manifestations depend upon the location of microfilariae and adult worms in the tissues. Of the eight filarial species that infect humans, Loa loa, Onchocerca volvulus, Wuchereria bacrofti, and Brugia malayi are associated with kidney disease. Loiasis is prevalent in West and Central Africa and manifests with localized allergic inflammation and swelling. Onchocerciasis (river blindness) is characterized by subcutaneous nodules, a pruritic skin rash, sclerosing lymphadenitis, and ocular lesions. Bancroftian and Table 21.11.2 Clinicopathological classification of schistosomal glomerulopathy Class I II III A IIIB IV V Light microscopic pattern Mesangioproliferative Exudative Mesangiocapillary type I Mesangiocapillary
type II Focal and segmental glomerulosclerosis Amyloidosis (a) ‘Minimal lesion’ (b) Focal proliferative (c) Diffuse proliferative Immunofluorescence Mesangial IgM and C3. Schistosomal gut antigens Endocapillary C3 Schistosomal
antigens Mesangial IgG, IgA, and C3, schistosomal gut antigen Mesangial and subepithelial IgG and C3, schistosomal gut antigen (early), IgA
(late) Mesangial IgG, IgM, and IgA Mesangial IgG Asymptomatic
proteinuria +++ – + + + + Nephrotic syndrome + +++ ++ +++ +++ +++ Hypertension ± – ++ + +++ ± Progression to endstage renal disease ± ± ++ ++ +++ +++ Response to treatment ± +++ – – – – Modified with permission from Barsoum R, Kidney Int 1993.

section 21 Disorders of the kidney and urinary tract 5056 brugia infections cause febrile episodes associated with acute lymph- angitis and lymphadenitis, leading to lymphoedema manifesting as hydrocele and elephantiasis. This form of filariasis is endemic in Africa and South and South-East Asia. Filarial nephropathy Clinical features Urinary abnormalities have been described in 11 to 25% of cases of loiasis and onchocerciasis, with nephrotic syndrome in 3 to 5%. In a survey in an endemic area, proteinuria was detected in over 50% of patients with lymphatic filariasis, with 25% showing a glomerular pattern of protein loss. The frequencies of proteinuria, nonvisible haematuria, and hypertension are significantly higher in patients with chronic sclerosing filariasis than in those with an acute febrile illness or microfilaraemia. False-positive rheumatoid factor and anti-DNA and antiphospholipid antibodies have been described. Pathology Light microscopy reveals a gamut of lesions, including minimal- change disease and focal segmental glomerulosclerosis, and mesangial proliferative, mesangiocapillary, and chronic sclerosing glomerulonephritis. Diffuse basement membrane thickening with endocapillary proliferation is the commonest finding. Mononuclear interstitial infiltration and microinfarcts around blood vessels have been demonstrated in patients with loiasis. Microfilariae may be found in the glomerular capillary lumina (Fig. 21.11.7), tu- bules, and interstitium. Electron microscopy shows widely spaced subepithelial, subendothelial, and intramembranous deposits and spikes. O. volvulus and B. malayi antigens, along with IgM, IgG, and

C3 have been demonstrated. Pathogenesis Glomerulonephritis is likely immune complex mediated. The levels of circulating immune complexes correlate with the adult worm burden. Dogs infected with Dirofilaria immitis develop glomerular lesions similar to human filariasis: glomerular lesions developed after selective catheterization and infusion of D. immitis into one renal artery; the contralateral kidney either remained un- involved or showed minor lesions, suggesting in situ immune com- plex formation. Diethylcarbamazine treatment, by killing the parasite, may lead to antigen release into the circulation, thus exacerbating the immune process. A temporal relationship between the administration of this agent and the development of proteinuria has been noted. Management Good response to antifilarial therapy with diethylcarbamazine is ob- served in patients with non-nephrotic proteinuria and/or haema- turia. The response is inconsistent in those with nephrotic syndrome, when deterioration of renal function may continue despite clearance of microfilariae. Chyluria Lymphatic filariasis secondary to W. bancrofti or B. malayi infec- tions leads to fibrosis of lymph glands and dilatation of draining lacteals. Under pressure, the dilated retroperitoneal lacteals rup- ture into the low-pressure urinary system, leading to leakage of lymph in urine. The presentation is characterized by passage of milky white urine (Fig. 21.11.8), with or without haematuria. Patients complain of backache, probably caused by distended vessels. Formation of chylous clots may result in acute urinary retention. Prolonged chyluria results in the loss of protein, fat, and lympho- cytes in the urine, leading to hypoproteinaemia and lymphopenia. Urinalysis shows proteinuria, and—if the history of change in urine colour is not elicited—an erroneous diagnosis of nephrotic syn- drome might be made, prompting an unnecessary kidney biopsy. About 80% of cases respond to treatment with diethylcarbamazine and dietary modification. Sclerotherapy using local instillation of povidone iodine, hypertonic dextrose, or silver nitrate is required for resistant cases (or less commonly surgery). Fig. 21.11.6 Plain radiograph of a patient with S. haematobium infection showing calcification of bladder wall. Courtesy of Professor R. Barsoum. Fig. 21.11.7 Photomicrograph of a kidney biopsy showing microfilariae with parallel-arranged nuclei throughout their length and covered by a sheath on their external aspect in the glomerular capillary lumen in a patient with lymphatic filariasis (arrows) (periodic acid–Schiff stain, magnification ×100).

21.11 Renal diseases in the tropics 5057 Renal disease in leprosy Leprosy is a chronic granulomatous disorder caused by the acid-fast bacillus Mycobacterium leprae. Nephritis was an important cause of death until the 1950s, but is now rare. The main renal lesions en- countered are glomerulonephritis, secondary amyloidosis, and tubulointerstitial nephritis. Glomerulonephritis The incidence of glomerulonephritis in leprosy is now less than 2%, but old autopsy series showed lesions in over 50% of cases. Most cases are seen in patients with multibacillary disease and during epi- sodes of erythema nodosum leprosum. Clinical presentation may be as nephrotic syndrome, acute nephritic syndrome, or rapidly pro- gressive renal failure. Hypocomplementaemia is common, and cir- culating cryoglobulins may be present. Mesangial proliferative and diffuse proliferative glomeruloneph- ritis are the commonest histological lesions. Electron microscopy reveals electron-dense deposits in the mesangial and subendothelial regions, focal foot-process widening, glomerular capillary basement membrane reduplication with mesangial interposition, and endothe- lial cytoplasmic vacuolation. Immunofluorescence reveals granular IgG and C3 deposits in the mesangium and along capillary walls. Circulating immune complexes can be detected in 30 to 75% of patients, and can be of mycobacterial origin or dapsone:antidapsone antibodies. Alternate pathway complement activation by cryopre- cipitates can also contribute. Steroids or antileprosy drugs have no effect on the course of glomerular disease. Prednisolone may hasten the recovery of

renal function in patients with renal failure during episodes of erythema nodosum leprosum. Amyloidosis Amyloid was documented in 55% of cases in older autopsy and bi- opsy studies in leprosy cases from the United States of America, 31% from Brazil, and less than 10% from Mexico, Africa, and India. The amyloid is of AA type and is far more frequent in lepromatous than nonlepromatous leprosy. Erythema nodosum leprosum further in- creases the risk as each episode is associated with a marked elevation of serum amyloid A protein. Patients with tuberculoid leprosy who have long-standing and infected trophic ulcers can also develop this complication. Renal disease in tuberculosis Tuberculosis is endemic throughout the tropics. Concerted efforts to contain the disease have been thwarted by the HIV epidemic and treatment default, leading to a rise in drug-resistant disease. Seen in less than 10% of all cases with tuberculosis, urinary tract involve- ment is a relatively late manifestation of disease. Common presenting features are irritative lower urinary symp- toms suggestive of infection as a result of ureteric and bladder in- volvement secondary to seeding of M. tuberculosis into the urine. Urinalysis shows pus cells, but cultures are repeatedly sterile. The presence of sterile pyuria or failure of symptoms to respond to conventional antibacterial treatment should raise the possibility of urinary tract tuberculosis. Systemic symptoms like fever, night sweats, and weight loss are helpful diagnostic clues when present. Only about one-third of patients show simultaneous pulmonary involvement. Involvement of renal parenchyma takes the form of granuloma- tous interstitial nephritis and caseous destruction, culminating in small nonfunctioning and often calcified kidneys. An association with glomerulonephritis was postulated in the pre-antibiotic era, but only occasional recent reports have described immune com- plex glomerulonephritis and dense-deposit disease in tuberculosis. A well-known complication, however, is amyloidosis, which is still seen in a significant proportion of patients in poor countries where the disease remains untreated for long periods. Once established, the course of amyloidosis is unaffected by treatment of the underlying tuberculosis. Imaging (Fig. 21.11.9) provides important diagnostic clues, with about 30% showing dystrophic calcification of the urinary tract (bladder and ureteric walls, or—less commonly—renal paren- chyma). Involvement of the excretory system is delineated better by intravenous urography, CT, or magnetic resonance imaging which shows thickening, irregularity or narrowing of involved segments, and cavities or mass effects secondary to necrosis. Fibrosis and (a) (b) Fig. 21.11.8 Panel (a) shows milky white urine in a patient with chyluria secondary to lymphatic filariasis and panel (b) shows filling up of ruptured lacteals on retrograde pyelogram.

 contraction of the bladder gives rise to reduction in capacity—the classical ‘thimble bladder’. Extrarenal spread can also be identified on imaging. Patients with advanced and bilateral disease have a reduced glom- erular filtration rate due to generalized destruction of the paren- chyma, but a more common cause for renal failure is urinary tract obstruction due to scarring of the lower tract. Management requires institution of antitubercular therapy ac- cording to local guidelines. Obstructive lesions that fail to respond to therapy require surgical correction, including urinary diversion and bladder augmentation surgery. Renal disease caused by leptospirosis Leptospirosis, the most widespread zoonosis in the world, is an occupational hazard in fishermen, coal miners, and sewage, ab- attoir, and farm workers throughout the tropics. The pathogenic Leptospira interrogates complex has 30 serogroups and 240 sero- types. Leptospira are shed in the urine by the animal hosts (rats, mice, gerbils, hedgehogs, foxes, dogs, cattle, sheep, pigs, and rabbits) and survive for several weeks in a moist environment. Human infec- tion occurs upon exposure of abraded skin and exposed mucosae to contaminated water, soil, or vegetation. Clinical features Leptospirosis occurs in both sexes and in

all age groups. The inci- dence peaks during or soon after the rainy season, especially fol- lowing floods. The disease starts with fever, chills, headache, severe muscle aches and tenderness, and dry cough, which terminate with defervescence after 4 to 10 days. Organ involvement is seen in the second phase and takes the form of AKI, cholestatic jaundice, and haemorrhagic manifestations (Weil's syndrome). AKI occurs in 20 to 85% of cases and is oliguric in 40 to 60%. It is typically mild and nonoliguric in anicteric patients. Renal magne- sium and phosphate wasting is common. Diuresis ensues by the end of the second week, and may last longer than that associated with other causes of AKI. Recent studies suggest that leptospiral infection can persist in hu- mans and may have long-term adverse effects on kidney function. Molecular techniques have shown asymptomatic urinary shedding of leptospira in areas of high disease transmission, including in those without serological evidence of recent infection. In a recent population-based study, individuals with previous leptospira ex- posure had a higher prevalence of CKD stages 3 to 5. Further, those with a higher antibody titre showed a greater decline in estimated glomerular filtration rate on follow-up. Diagnosis Diagnosis is based on culture or serology. The organisms can be grown on Fletcher's or Stuart's semisolid media from blood during the first phase, and later from urine. Antileptospiral antibodies are detectable in the second phase. A single titre of greater than 1:400 or a fourfold increase is taken as significant. A macroscopic agglutination test or a slide test can be used to screen patients, but these are not specific. The gold standard is the complex microscopic agglutination test that requires maintenance of live leptospira cultures. Other tests include an IgM-specific dot enzyme-linked immunosorbent assay (ELISA), complement fixation, serum and salivary ELISA, rapid IgM dipstick ELISA, and gold immunoblot tests. Lately, nucleic acid-based testing has allowed identification of greater number of cases. Pathology Grossly, the kidneys are swollen and bile stained. The main light- microscopic lesion is a tubulointerstitial nephritis, with mono- nuclear cells and eosinophilic infiltration. Mild and transient mesangial proliferative glomerulonephritis with C3 and IgM depos- ition is occasionally noted. Pathogenesis Renal involvement results from direct invasion of the renal tissue by the organism and liberation of bacterial enzymes, metabol- ites, and endotoxins. Addition of leptospira endotoxin to human macrophages induces release of tumour necrosis factor-α (TNFα). Proximal convoluted tubules show a decrease in expression of so- dium/hydrogen exchanger isoform 3, aquaporin 1, and α-Na+,K+- ATPase. The glycoprotein component of the endotoxin inhibits the renal Na+,K+-ATPase and apical Na+–K+–Cl− cotransporter, leading to potassium wasting. Leptospiral outer membrane proteins have been localized to the proximal tubules and interstitium of infected animals. Recent studies have suggested the involvement of Toll-like receptor, leading to activation of NF-κB and mitogen-activated pro- tein kinases, and enhanced message for inducible nitric oxide syn- thase, monocyte chemoattractant protein-1 and TNFα. Leptospiral outer membrane proteins may also induce activation of the trans- forming growth factor-β/SMAD-associated fibrosis pathway, leading to accumulation of extracellular matrix. Management Leptospirosis is a self-limiting disease, and mild cases recover spon- taneously. The emphasis is on symptomatic measures, together with correction of hypotension and fluid and electrolyte imbalance. Antibiotic therapy can shorten the duration of fever and hasten amelioration of leptospiruria. Adverse prognostic factors include

Fig. 21.11.9 Intravenous pyelogram in a patient with renal tuberculosis. The left kidney is hydronephrotic and the right kidney is nonfunctioning and shows punctuate calcification of the dilated pelvicalyceal system. Courtesy of Professor John Eastwood.

advanced age, pulmonary complications, hyperbilirubinaemia, diarrhoea, hyperkalaemia, and the presence of other infections. Kidney injury

in scrub typhus Scrub typhus, caused by Orientia tsutsugamushi, a Gram-negative α-proteobacterium of family Rickettsiaceae, is endemic in Asia, with an estimated 1 million cases occurring annually. The infection is maintained in nature by transovarian transmission in trombiculid mites. Human involvement occurs when people get bitten by in- fected larvae, leading to inoculation of organisms into the skin. The World Health Organization identifies scrub typhus as a re- emerging disease in South-East Asia and the South-Western Pacific region, with a fatality rate of 30% in untreated cases. Until recently, renal involvement due to scrub typhus had not received much at- tention, and a recent systematic review could only find a few case reports specifically describing AKI. However, recent studies from India have shown renal abnormalities in 70 to 80% of cases, and about 50% exhibit AKI, which is an independent predictor of mor- tality. Vascular endothelial cell injury is thought to be the pre- dominant mechanism. Renal biopsies have shown mild mesangial hyperplasia, acute tubular necrosis, or tubulointerstitial nephritis. Other infective causes of renal disease Zygomycosis Zygomycosis (syn. mucormycosis) is an opportunistic infection caused by the saprophytic fungi of the order Mucorales and genera Rhizopus, Absidia, and Rhizomucor. The spores gain entry into the body through inhalation or cutaneous breach. The fungus primarily spreads through vascular route, leading to thrombosis of large and small arteries and infarction and necrosis of the affected organ. Primary renal zygomycosis has been described from several tropical countries. Patients present with high fever, lumbar pain, pyuria, and oliguric AKI. The initial route of entry of the organism is often uncertain. Diagnosis requires a high index of suspicion and use of imaging. Ultrasonography reveals enlarged kidneys. CT scan appearance is often diagnostic and shows large kidneys with perinephric stranding, large nonenhancing areas indicating infarction (Fig. 21.11.10), along with perirenal and/or intrarenal abscesses. Characteristic broad, aseptate hyphae can be demon- strated in material obtained by needle aspiration or biopsy. The only definitive treatment is extensive debridement of affected tissue, which may include bilateral nephrectomy and systemic amphotericin B therapy. This condition carries an extremely poor prognosis. HIV infection Most individuals affected with HIV infection live in the tropical countries of Africa and South Asia. The frequency of renal involve- ment varies widely in different geographic areas and races, with less than 5% in Asia and Latin America and 25 to 50% in Africa. Renal lesions can be as a direct result of the HIV infection, or indirectly secondary to treatment or associated conditions (Table 21.11.3 and Fig. 21.11.11). Fig. 21.11.10 Contrast-enhanced CT of the abdomen showing almost complete nonenhancement of the left and minimal patchy contrast enhancement of the right renal parenchyma (suggesting infarction), along with bilateral perinephric stranding (arrows) in a patient with AKI due to bilateral mucormycosis. Table 21.11.3 Renal manifestations in of HIV infection Direct renal effects associated with HIV infection Acute kidney injury • Volume loss (e.g. gastroenteritis, pancreatitis) • Infections • Myocardial dysfunction (e.g. cardiomyopathy) • Liver failure (HIV cholangiopathy or coinfection with hepatitis B and/or C); hepatorenal syndrome Chronic kidney disease • HIV-associated nephropathy (HIVAN) • HIV immune complex glomerulonephritis Electrolyte and acid–base disorders • Hyponatraemia (related to SIADH, volume depletion, and adrenal insufficiency) • Hypernatraemia (related to dehydration) • Hyperkalaemia (related to renal dysfunction, trimethoprim, or IVI pentamidine use and adrenal insufficiency) • Hypokalaemia (related to diarrhoea and amphotericin B therapy) • Metabolic acidosis (lactic acidosis secondary to tissue hypoperfusion, stavudine use or liver disease or kidney failure) Indirect renal involvement Acute kidney injury • Toxins, especially traditional herbal medications • Analgesics, especially nonsteroidal anti-inflammatory drugs • Antiretroviral agents, especially tenofovir (tubular toxicity), ritonavir (exacerbates tenofovir nephrotoxicity), indinavir (crystal

formation and obstruction), and stavudine (lactic acidosis and/or pancreatitis) Chronic kidney disease • Metabolic syndrome associated with
antiretroviral drug use • Other chronic kidney disease with incidental HIV infection IVI, intravenous infusion; SIADH, syndrome of inappropriate antidiuretic hormone secretion. Reproduced with permission from Naicker S, Paget G. HIV and renal disease. In: Turner N, Lameire N, Goldsmith DJ, et al. Oxford Textbook of Clinical Nephrology. 4th ed. Oxford: Oxford University Press (2015).

section 21 Disorders of the kidney and urinary tract 5060 The presentation of renal disease in HIV infection is the re- sult of a complex interplay between the pheno- and/or genotypic variants of the virus, the genetic make-up of the host, and envir- onmental factors. The viral genes nef and var increase podocyte proliferation and dedifferentiation, and alter podocyte protein expression. HIV-1 infection induces tubular injury by triggering an apoptotic pathway involving caspase activation and FAS up- regulation. Release of a variety of cytokines also affects podocytes and tubular cells. HIV-associated nephropathy also shows a strong genetic pre- dilection: people of African ancestry exhibit a 20-fold increase in relative risk compared with individuals of Caucasian descent. The differential risk has been traced to the presence of pathogenic vari- ants of MYH9 and APOL1 gene variants in this population. A number of studies have shown a direct link between the viral load and development as well as progression of kidney disease. Use of highly active retroviral therapy has had a favourable effect on dis- ease course. Toxic causes of renal disease in the tropics
Snake venoms Most of the 450 venomous snake species are found in the tropical and subtropical regions. Renal lesions have been reported following bites by snakes belonging to classes Viperidae (Russell’s viper, saw- scaled viper, puff adder, pit viper, and rattlesnakes), Colubridae (boomslang, Bothrops jararaca, gwardar, dugite, and Cryptophis nigrescens), and Hydrophidae (sea snakes). AKI is the most fre- quent and clinically important effect of envenomation on the kid- neys, with most cases seen following viper and sea snake bites. In India, about 13 to 32% of those bitten by Echis carinatus (Russell’s viper) develop AKI. The reported incidence from other countries varies between 1 and 27%. Clinical features The initial symptoms are pain and swelling of the bitten part, fol- lowed by blister formation and ecchymosis. Bleeding—as ooze from fang marks, haematemesis, melaena, or haematuria—is seen in 65% of cases. Sea-snake bites cause myonecrosis, which manifests as muscle pains and weakness. Renal failure sets in from within a few hours to as late as 4 days after the bite, and is usually oliguric. A history of passage of ‘Coca- Cola’-coloured urine, indicating intravascular haemolysis, is obtained in about one-half of cases, and over 90% show oliguria. Life-threatening hyperkalaemia may develop in patients with haem- olysis or myonecrosis. With effective management, oliguria resolves in 5 to 21 days; persistence indicates the likelihood of renal cortical necrosis (Fig. 21.11.12). Pathology Grossly, the kidney are swollen and exhibit petechial haemorrhages. Light microscopy shows acute tubular necrosis in 70 to 80% of cases. Interstitial oedema, inflammatory cell infiltration, and scat- tered haemorrhages may be seen. Electron microscopy reveals dense intracytoplasmic bodies in the proximal tubules representing degen- erated organelles. Other lesions include acute interstitial nephritis, thrombotic microangiopathy, necrotizing arteritis, and crescentic glomerulonephritis. Acute cortical necrosis is seen in 20 to 25% of cases. Pathogenesis Renal damage is a cumulative effect of direct nephrotoxicity of venom, hypovolaemia, haemolysis, myoglobinuria, and dissemin- ated intravascular coagulation. Injection of snake venom leads to increased excretion of tubular enzymes in rats. Administration of Russell’s viper venom led to a dose-dependent decrease in inulin clearance in isolated perfused rat kidney. Destruction of the glom- erular filter, lysis of vessel

walls, mesangiolysis, and tubular injury have been shown in experimental models. A vasculotoxic factor has been isolated from the venoms of several snakes. Similarities have been noted between the structure of the potent vasoconstrictor endothelin-1 and the venom of the Israeli burrowing asp. Fig. 21.11.11 Photomicrograph of a patient with HIV-associated nephropathy showing glomerular collapse, focal sclerosis, and microcytic dilatation of tubules. Reproduced with permission from Naicker S, Paget G. HIV and renal disease. In: Turner N, Lameire N, Goldsmith DJ, et al. Oxford Textbook of Clinical Nephrology. 4th ed. Oxford: Oxford University Press (2015). Courtesy of Prof Stewart Goetsch, University of the Witwatersrand. Fig. 21.11.12 Contrast-enhanced CT of the abdomen in a patient with AKI following an Echis carinatus bite showing acute cortical necrosis. The nonenhancing zone of necrotic cortex is limited by the enhancing subcortical rim on the outside (arrows) and the medulla on the inside (arrowheads).

21.11 Renal diseases in the tropics 5061 Hypotension and circulatory collapse can result from blood loss, release of kinins, or depression of the medullary vasomotor centre or myocardium. Kininogenases are present in crotalid venom. Viper palastinae venom produces depression of the medul- lary vasomotor centre, whereas Bitis arietans venom causes myo- cardial depression, arteriolar dilatation, and increased vascular permeability. Phospholipase A and a basic protein called ‘direct lytic factor’ present in Russell’s viper and E. carinatus venoms cause intravas- cular haemolysis and disseminated intravascular coagulation. Microangiopathic haemolytic anaemia can develop following A. rhodostoma, Russell’s viper, E. carinatus, puff adder, and guarder bites. Viper venom activates the coagulation cascade at several levels, leading to rapid thrombin formation. Management The mainstay of management is prompt antivenom administration to cases with evidence of systemic envenomation or local inflam- mation involving more than 50% of the limb circumference. There is no agreement on the exact dose needed, or duration of therapy. A rule of thumb is to continue administration until the effects of systemic envenoming disappear as shown by normalization of the whole-blood clotting time. Concomitant measures include re- placement of lost blood, maintenance of electrolyte balance, ad- ministration of tetanus immunoglobulin, and adequate treatment of pyogenic infection. Maintenance of a high urinary output, as well as alkalinizing the urine, may attenuate renal damage in those with haemolysis. Other animal toxins Bee, wasp, and hornet stings Stinging insects belonging to the order Hymenoptera, such as honeybees, yellow jackets, hornets, and paper wasps, are found in most tropical countries. Systemic symptoms develop when an in- dividual is attacked by a swarm of insects and receives a large dose of venom. Manifestations include vomiting, diarrhoea, hypotension, and loss of consciousness. AKI is secondary to haemolysis, rhabdo- myolysis, or both. Haemolysis results from the action of a basic pro- tein fraction, melittin, and phospholipase A. Rhabdomyolysis has been attributed to polypeptides, histamine, serotonin, and acetyl- choline. Experimental studies have suggested a direct nephrotoxic role of venom components. Renal biopsy invariably reveals acute tubular necrosis. Carp and sheep bile Acute hepatic and renal failure have been reported following con- sumption of the raw gallbladder or bile of freshwater and grass carps (Ctenophryngodon idellus, Cyprus cardio, Hypophythalmichthys molitrixn, Mylopharyngodon pisces, and Aristichthys nobles) in Taiwan, South China, Hong Kong, Japan, India, and South Korea, and sheep bile in the Middle East. Initial symptoms include abdom- inal pain, nausea, vomiting, and watery diarrhoea. Hepatocellular jaundice and AKI occur 48 h after ingestion. Haematuria is noted in 75% of cases. The duration of renal failure ranges from 2 to 3 weeks. Manifestations vary depending upon the varieties of carp and amount of bile ingested. Histology reveals acute tubular necrosis and interstitial oedema. Other conditions AKI has been reported following stings by scorpion, jellyfish,

and giant centipede. Scorpion stings result in disseminated intravascular coagulation and internal bleeding, and these can give rise to intra- vascular haemolysis. Plant toxins Tropical communities consume products derived from locally grown plants, either as food or as medicines, and many of these con- tain nephrotoxic substances. Exposure may be accidental, when a toxic plant is mistaken for an edible one. The insult can be identified quickly when the presentation is acute, but the cause–effect rela- tionship may be harder to establish in the case of slowly progressive kidney disease. Traditional medicines constitute a special class of nephrotoxins among poor populations in tropical Africa and Asia. In African hos- pitals, more than 75% of all deaths from acute poisoning and 25 to 60% of all AKI from medical causes are due to traditional medicines. These agents are obtained from traditional healers ('witch-doctors'), who wield considerable power. Administration is either by the oral route or as enemas, the latter consisting of mixtures of herbs, barks, roots, leaves, and bulbs, administered through a truncated cow's horn or hollow reed. Increasing urbanization and industrialization have introduced potent chemicals (e.g. paint thinners, turpentine, chloroxylenol, ginger, pepper, soap, vinegar, copper sulphate, and potassium permanganate) into their armamentarium. AKI has been reported following the use of such enemas: detailed studies are not available, but histology usually shows acute tubular necrosis. Callilepis laureola (impila) poisoning C. laureola, a herb with a tuberous rootstock, grows in several coun- tries in sub-Saharan Africa. An extract of the tubers is taken orally or as an enema as a traditional remedy, and is a common cause of AKI in the black South African population. Symptoms appear within 24 h in 40% and within 4 days in 70% of patients. Children and older people show earlier and more severe abnormalities. Abdominal pain and vomiting are followed by hypoglycaemia, convulsions, and jaundice. Histology shows acute tubular necrosis and/or interstitial infiltration. Atractyloside, an alkaloid in the tuber of the plant, in- hibits ATP synthesis and is believed to have nephrotoxic and hypo- glycaemic effects. Gastrointestinal fluid loss contributes to the renal dysfunction. Treatment is supportive and includes correction of hypoglycaemia and volume and electrolyte replacement. The mor- tality rate is over 50%. Djenkol bean poisoning Djenkol beans (Pithecolobium lobatum and P. jiringa, family Mimosaceae) are considered a delicacy in Indonesia, Malaysia, southern Thailand, and Myanmar (Burma). AKI can occur when raw beans are consumed in large amounts with low fluid intake, and nephrotoxicity has been reported most commonly in the rainy season from Malaysia and Indonesia. Symptoms include dysuria, lumbar pain, hypertension, haematuria, and oligoanuria. The breath and urine emit a characteristic sulphuric odour. Urinalysis shows needle-like crystals of djenkolic acid, a sulphur-rich cysteine thioacetal of formaldehyde that forms in the concentrated acidic urine of the distal tubules. Individual susceptibility to the toxic

 effects is variable, possibly related to hydration status or variability in activity of metabolizing enzymes. High fluid intake and urinary alkalinization helps in dissolving the crystals. Most victims recover within a few days. Chronic ingestion can lead to development of djenkolic acid stones. Mushroom poisoning Less than 1% of all mushrooms are toxic. AKI has been observed following the ingestion of mushrooms of the genera Amanita, Galleria, Cortinarius, and Inocybe. Amanita phalloides (death cap) and A. virus (destroying angel) grow commonly in lawns, pastures, on living trees, in basements, plasterboard walls, and flower pots, and may be picked and ingested by inexperienced collectors and children. Initial symptoms are related to the gastrointestinal tract and may result in dehydration and hypotension. The toxic com- pounds (phallotoxin, amatoxin) inhibit RNA polymerase. Hepatic and renal failure develops after a couple of days. Renal histology shows acute tubular necrosis.

Management is supportive; charcoal haemoperfusion is effective in clearing α-amanitin from circulation and may improve outcome. Overall mortality is over 50%, and ex- ceeds 70% in children. Long-term ingestion of cortinarius mushrooms has been impli- cated in chronic renal failure. Details of other toxic plants that have been associated with development of kidney diseases are described in Table 21.11.4. Chemical nephrotoxins Increasing industrialization has facilitated the access of the poor and poorly educated populations of tropical countries to a variety of chemicals. Poisonings have been reported after accidental inges- tion or following attempted suicide or homicide. AKI is a manifest- ation of toxicity of many of these agents, such as copper sulphate, ethylene glycol, paraphenylenediamine (PPD), paraquat, ethylene dibromide, and hexavalent chromium compounds. Ethylene glycol Ethylene glycol is used as an organic solvent, antifreeze, preservative, and glycerine substitute. It is metabolized in the liver to glyoxylic acid and oxalate, which combines with calcium and gets deposited in the acid milieu of renal tubules as calcium oxalate crystals, leading to AKI. Epidemics of ethylene glycol poisoning in children as a result of substitution of nontoxic propylene glycol with toxic di- and poly- ethylene glycols as a vehicle in paediatric syrup preparations have been reported from tropical countries including India, Bangladesh, Nigeria, South Africa, and Haiti. The mortality is high due to underlying diseases and delayed diagnosis: 236 deaths were re- corded among 339 children with AKI in Bangladesh during one such epidemic. Paraphenylenediamine PPD is a widely used chemical in Africa, Middle East, and Indian subcontinent as a textile, fur, or hair dye, to colour cosmetics, for temporary tattoos, photographic development, and in gasoline. It is a well-known skin irritant and may be absorbed from the skin. Being cheap and widely available, it is also used for suicidal pur- poses. Clinical manifestations include cervicofacial oedema, chocolate brown-coloured urine, oliguria, muscular oedema, and shock. The most common renal presentation is as oliguric AKI, perhaps secondary to direct toxicity, rhabdomyolysis, and hypovol- aemia, and PPD toxicity is a common cause of AKI in parts of the Indian subcontinent and Africa. Treatment is mostly supportive. Antihistamines and steroids are used in the management of airway oedema. Alkaline diuresis is tried in those with myoglobinuria. PPD is not dialysable. Copper sulphate Copper sulphate is commonly used as a pesticide, in the leather in- dustry, and in making home-made glue. Its blue colour makes it at- tractive to children, with risk of inadvertent poisoning, and it is used for suicidal purposes in the Indian subcontinent. Initial symptoms of copper sulphate poisoning consist of a metallic taste, increased salivation, burning retrosternal pain, nausea, vomiting, diarrhoea, haematemesis, and melaena. Jaundice, hypotension, convulsions, and coma indicate severe poisoning. Acute pancreatitis, myoglobinuria, and methaemo- globinaemia have also been reported. Oliguric AKI develops in 20 to 25% of cases and is frequently associated with passage of dark (Coca-Cola)- coloured urine, indicating intravascular haemolysis, the risk of which is increased in genetic G6PD defi- ciency. Renal histology shows acute tubular necrosis with abun- dant pigmented haemoglobin casts indicating haemoglobinuria. Acute cortical necrosis occurs rarely. Dialysis may be required for renal failure, but is ineffective in clearing copper from the body. Future challenges In the coming years, tropical societies will face major impacts of climate change and water scarcity on kidney health. Changes in air and ocean temperature will make their impact felt in the tropics during the course of next 10 years, long before changes are noted in the temperate regions. Temperatures in excess of 50°C are already being recorded regularly in the tropics. The number of tropical cyclones is rising year on year. According to the United Kingdom-based risk analysis firm Maplecroft, the top 10 countries at ‘extreme risk’ from climate change are all tropical countries. The kidneys are particularly vulnerable to the effects of climate change. Dehydration secondary to heat stress will increase the risk of acute as well as chronic kidney injury. Unpredictable rainfall, as seen in the

Indian state of Tamil Nadu in 2015, is likely to lead to the re-emergence of water-borne and vector-borne infectious diseases, nullifying the past gains made in infection control. Changes in climate and biodiversity have been linked to increases in zoonotic and vector-borne disease outbreaks. Changes in vector ecology and water quality will increase the risk of the re-emergence of previously contained infections or of the emergence of new in- fections in the tropics. Potential changes in the virulence of organ- isms is also a possibility, as shown by the emergence of kidney injury in vivax malaria, once considered benign, and of kidney injury in scrub typhus. Degradation of the ecosystem, with air and water pol- lution, will increase the risk of exposure to environmental toxins.

21.11 Renal diseases in the tropics 5063 A decreased ability to excrete, secondary to dehydration, will lead to higher concentrations of such toxins in the kidney, with adverse consequences on kidney health. Combating these challenges will require concerted action on medical as well as societal and political fronts. Anticipating the upcoming challenges and fortifying the health system to address these in a timely manner is a challenge that needs to be tacked urgently. FURTHER READING Araujo ER, et al. (2010). Acute kidney injury in human leptospir- osis: an immunohistochemical study with pathophysiological cor- relation. Virchow Arch, 456, 367–75. Barber BE, et al. (2013). A prospective comparative study of knowlesi, falciparum, and vivid malaria in Sabah, Malaysia: high proportion with severe disease from Plasmodium knowlesi and Plasmodium Table 21.11.4 Plant nephrotoxins in the tropics Plant Reported from Active molecule Renal manifestations Other manifestations Averrhoa bilimbi (irumban puli) South India Oxalic acid Intratubular obstruction Averrhoa carambola (star fruit) Hong Kong, Taiwan Oxalate Intratubular precipitation of oxalate crystals Vomiting Callilepis laureola (impila) Sub-Saharan Africa Atractyloside ATN Abdominal pain, diarrhoea, vomiting, jaundice, seizures, and coma Catha edulis (khat leaf) East Africa, Arab peninsula S-cathione, ephedrine ATN Hepatotoxicity Cleistanthus collinus (oduvan) India Cleistanthin A and B, collinusin, diphylline AKI Hypotension, hypokalaemia, arrhythmia Colchicum autumnale (meadow saffron) Turkey Colchicine ATN Haemorrhagic gastroenteritis, muscle paralysis, respiratory failure Crotalaria laburnifolia (bird flower) Zimbabwe, Sri Lanka Pyrrolizidine alkaloids ATN, HRS Hepatic veno-occlusive disease, pulmonary injury, thrombocytopenia Cupressus funebris Endl (mourning cypress) Taiwan Flavonoid ATN, AIN AHF, haemolytic anaemia, thrombocytopenia Dioscorea quartiniana and D. quinqueloba (yam) Africa, Asia Dioscorine, dioscin ATN Convulsions, encephalopathy Dodonaea angustifolia (sand olive) South Africa Unknown AIN Pulmonary embolism Euphorbia metabelensis, E. paralias (spurge) Zimbabwe Irritant chemicals in plant latex ATN Thrombocytopenia Glycyrrhiza glabrata (liquorice) Several countries Glycyrrhizic acid ATN Rhabdomyolysis, hypokalaemia, hypertension, cardiac arrhythmia Larrea tridentate (chaparral) Chile, South Africa Nordihydroguaiaretic acid, s-quinone Renal cysts, renal cell carcinoma Hepatic failure Lawsonia alba (henna) Middle east, North Africa, Pakistan 2-hydroxy-1,4- naphthoquinone ATN Haemolysis Pithecolobium lobatum and Pithecolobium jiringa (djenkol) beans South East Asia Djenkolic acid Intratubular obstruction and ATN Lumbar and lower abdominal pain, hypertension Propolis Brazil, Taiwan Unknown AIN Contact dermatitis Rhizoma rhei Hong Kong Anthraquinones (emodin, aloe-emodin) AIN None Securidacea longepedunculata (violet tree, wild wisteria) Congo, Zambia, Zimbabwe Methylsalicylate, securinine, saponins ATN Vomiting, diarrhoea Sutherlandia frufesces (cancer brush), Dodonaea angustifolia South Africa Unknown AIN Pulmonary embolism Takeout roumia Morocco, Sudan Paraphenylenediamine ATN Rhabdomyolysis Taxus celebia (Chinese yew) Asia Flavonoid ATN, AIN Hepatitis, haemolysis, DIC Thevetia peruviana (yellow

oleander) India, Sri Lanka Cardiac glycosides ATN, mesangiolysis Liver failure, cardiac arrhythmias Tribulus terrestris USA, Iran Unknown ATN, AIN Liver failure, encephalopathy Tripterygium wilfordii Hook F
(thunder god vine) Taiwan Triptolide ATN Diarrhoea, shock Uncara tomentosa (cat's claw) Peru Alkaloids, flavonols AIN Diarrhoea, hypotension, bruising, bleeding gums AHF, acute hepatic failure; AIN, acute interstitial nephritis, AKI, acute kidney injury; ATN, acute tubular necrosis, DIC, disseminated intravascular coagulation; GI, gastrointestinal; HRS, hepatorenal syndrome.

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ESSENTIALS There are more than 200 inherited disorders in which the kidney is affected. Many are single gene diseases that affect children, but cases are not restricted to paediatrics and diagnosis is often made in adults. They display a wide range of renal features: cystic, glomerular, tubulointerstitial, vascular, malformative, tumoural, and urolithiasis. Autosomal dominant polycystic kidney disease—affects about
1/1000 individuals and accounts for 7% of cases of endstage renal failure in Western countries. Inheritance is autosomal dominant, with mutations in polycystin 1 responsible for 75% of cases and mutations in polycystin 2 accounting for most of the remainder. May present with renal pain, haematuria, urinary tract infection, or hypertension, or be discovered incidentally on physical examination or abdom- inal imaging, or by family screening, or after routine measurement of renal function. Commonly progresses to endstage renal failure be- tween 40 and 80 years of age. Main extrarenal manifestations are intracranial aneurysms, liver cysts, and mitral valve prolapse. Alport's syndrome—X-linked dominant inheritance in 85% of kindreds, with molecular defects involving the gene encoding the α-5 chain of the type IV collagen molecule. Males typically pre- sent with visible haematuria in childhood, followed by permanent nonvisible haematuria, and later by proteinuria and renal failure. Extrarenal manifestations include perceptive deafness of variable se- verity and ocular abnormalities (bilateral anterior lenticonus is path- ognomonic). Carrier women often have slight or intermittent urinary abnormalities, but may develop mild impairment of renal function late in life, and a few develop endstage renal disease. In the auto- somal recessive form of Alport's syndrome, renal disease progresses to endstage before 20 to 30 years of age at a similar rate in both af- fected men and women. Hereditary tubulointerstitial nephritis—nephronophthisis is the most common genetic cause of endstage renal disease in chil- dren and young adults, and is a group of autosomal recessive tubulointerstitial nephropathies with multiple, small medullary cysts that appear late in the course of the disease. Eighty per cent of cases are caused by homozygous deletions of the NPH1 gene, which codes for nephrocystin. It presents with polyuria, polydipsia, and growth retardation in early childhood, progressing to endstage renal disease at a mean age of 14 years. In adults, autosomal dominant tubulointerstitial nephritis, sometimes with gout and medullary cysts, is related to mutations in various genes (UMOD, MUC1, REN, TCF2). Hereditary tumours—in von Hippel–Lindau disease, due to mu- tations in the tumour suppressor gene VHL, renal cysts and bilat- eral multifocal renal cell carcinomas are found in 70% of cases. Carcinomas are often asymptomatic, should be screened for regu- larly, and occur at a mean age of 45 years. In tuberous sclerosis, due to mutations in genes encoding hamartin (TSC1) or tuberin (TSC2), multiple and bilateral renal angiomyolipomas may bleed, or

induce progressive renal impairment. Autosomal dominant polycystic kidney disease and other cystic diseases of the kidneys An overview of the most frequent causes of cystic kidney diseases, genetic and nongenetic, is shown in Table 21.12.1. Autosomal dominant polycystic kidney disease Autosomal dominant polycystic kidney disease (ADPKD) is by far the most frequent inherited kidney disorder, accounting for approxi- mately 7% of cases of endstage renal failure in Western countries. It is one of the most frequent human inherited monogenic diseases (c.1 in 1000 individuals). Diagnosis The diagnosis of ADPKD is mainly based on renal imaging. Ultrasonography, inexpensive and safe, remains the imaging mo- dality of choice to make the diagnosis. One must take into account the presence or absence of a family history of ADPKD, the patient's age, the number of observed cysts, and their localization and morph- ology. If unsure, a genetic diagnosis is sometimes offered and differ- ential diagnoses must be explored. Positive diagnosis in a subject at risk of ADPKD This follows screening, usually of asymptomatic children and/or siblings of an affected individual who have a 50% risk of having inherited ADPKD. Paediatric complications of ADPKD are ex- ceptional and there is no proven benefit to screen for ADPKD in

children, and the psychological consequences of a positive diagnosis in children or adolescents are unknown. Thus, most nephrologists recommend checking blood pressure annually, but do not propose screening before 18 to 20 years of age. In relatives of a case, the diag- nosis of ADPKD is based on the presence of cysts on the kidney ultrasound. However, 'simple' renal cysts are not rare in the general population, and their prevalence increases with age. For the age group 15 to 39 years, an ADPKD diagnosis is made if there are three or more cysts (unilateral or bilateral), and between 40 and 59 years, at least two cysts on either side. ADPKD cannot be formally excluded before 40 years of age. These criteria ensure a positive and negative predictive value of 100% and are applicable to all patients regardless of ADPKD genotype. In the absence of these criteria, the presence of cysts is most often associated with banal multicystic kidney disease. Exclusion of diagnosis of ADPKD In a person at risk for ADPKD who wants to give a kidney to a relative or loved one, it is essential to rule out the diagnosis with certainty. Two tests may be applied: (1) genetic testing to be com- pared with the known family anomaly, and (2) a magnetic resonance imaging (MRI) scan, knowing that the negative predictive value of this test (no renal cyst) is almost perfect from the age of 16, at least to exclude PKD1-related disease. Absence of family history of ADPKD About 10 to 15% of patients with ADPKD have a negative family history. When ultrasound examination of one of the parents of the patient is positive, it is most often a late diagnosis of a mild form (a PKD2 gene mutation or a not truncating mutation of the PKD1 gene). If ultrasound examination of both parents is negative, a de novo mutation (about 5% of cases) is possible, as well as somatic mosaicism. Several elements plead in favour of ADPKD: • Negative differential diagnosis of other renal cystic disease (Table 21.12.2 and Figure 21.12.1) • Kidneys are increased in size with countless cortical and me- dullary cysts • Extrarenal cross-sectional (CT or MRI) imaging: presence of cysts in the liver, eventually the pancreas or spleen • Genetic testing (see Table 21.12.2) Renal ultrasonography in ADPKD See Fig. 21.12.1. Symptoms Renal manifestations In some patients, ADPKD is asymptomatic and discovered during family investigation, or by chance on abdominal ultrasonography. In most cases, however, there are symptoms and patients complain of one or more of the following at some time during their life: renal pain due to cyst development, or stone or blood clot migration; bleeding within a cyst, leading to flank pain, with the hyperdense

Fig. 21.12.1 Typical ultrasonographic appearances of ADPKD. The kidney is enlarged and contains

multiple cysts of different sizes. Reproduced with permission from Sandford R. Autosomal dominant polycystic kidney disease: diagnosis. In: Turner N, Lameire N, Goldsmith DJ, et al. Oxford Textbook of Clinical Nephrology. 4th ed. Oxford: Oxford University Press (2015). Copyright © 2015 Oxford University Press. Table 21.12.1 Conditions causing cystic kidney diseases Condition Characteristics Autosomal dominant diseases Autosomal dominant polycystic kidney disease Large kidneys (often), numerous diffuse renal cysts, hepatic cysts Von Hippel–Lindau (VHL) disease Large kidneys (often), cysts, solid lesions Tuberous sclerosis Large kidneys (often), cysts, angiomyolipomas TCF2 mutation (renal cysts and diabetes syndrome) Medullary cysts; cystic dysplasia ± urinary malformations ± diabetes (MODY type 5) UMOD, REN, MUC1 mutations Medullary cysts ± gout Medullary cysts TCF2, UMOD, REN mutations Autosomal dominant inheritance Recessive polycystic kidney disease, nephronophthisis Autosomal recessive inheritance Frequent nonhereditary multicystic diseases Renal multicystic disease Less than 5 simple cysts without kidney enlargement Tubulointerstitial nephritis Small medullary cysts (mostly seen on MRI) if impaired renal function Acquired cystic disease Patients with impaired renal function, often on dialysis Medullary sponge kidney (Cacchi—Ricci) Urolithiasis, nephrocalcinosis Parapelvic cysts Cysts limited to renal sinus Table 21.12.2 Diagnostic tests for ADPKD Test Age
(years) To affirm
ADPKD To exclude ADPKD Renal ultrasonography 15–39 ≥3 cysts (total) Impossible 40–59 ≥2 cysts in each kidney 0 or 1 cyst in each kidney Renal MRI

> 16 ≥10 cysts (total) <5 cysts Genetic testing (Adults) PKD1 or PKD2 mutation No PKD1/PKD2 mutation May be negative (somatic mosaicism?)

21.12 Renal involvement in genetic disease 5067 cyst fluid then being visualized by CT; bleeding into the urinary tract, with visible haematuria occurring in approximately 30% of cases; or fever due to upper urinary tract infection, which is more frequent in women, or to cyst fluid infection. Renal stones, pre- dominantly uric acid (for unknown reasons), develop in about 20% of the patients. Hypertension is a common and early finding in ADPKD, occurring in about 30 to 50% of patients with normal renal func- tion. Subsequently, with the development of renal failure, up to 80% of patients become hypertensive. Why hypertension develops is not known: it has been ascribed to compression and ischaemia of the normal renal parenchyma by cysts. Renal failure is also a common finding in ADPKD. When it occurs, it usually progresses to endstage at between 40 and 60 years of age. However, in 30% of cases it reaches endstage later, and in 5% earlier, including very rare instances when it develops in the first years of life. Recent epidemiological studies have indicated that ADPKD may have a much more indolent course in a substantial number of cases: 25 to 50% of affected subjects are not in endstage renal failure by 70 years of age, and some patients may reach 80 or 90 years without the need for renal replacement therapy. This information is crucial for genetic counselling. Genetic factors are major determinants of renal prog- nosis: the renal disease progresses more slowly in families with PKD2 disease (mean age at endstage renal disease 55 years in PKD1 disease, compared with >75 years in PKD2 disease). PKD1 disease progresses more slowly in women than in men. Control of hypertension may slightly reduce the rate of progression. Extrarenal manifestations Liver cysts develop in 70% of patients, usually later in life than renal cysts. They are more frequent and more diffuse in women than in men. They are usually asymptomatic but may be clinically palpable, and are typically detected by

ultrasonography. Liver function tests are usually normal. Liver cyst infection may occur, particularly in patients on dialysis or in transplant recipients. Massive liver involve- ment can cause severe discomfort in some cases, mostly in women. Cardiovascular abnormalities include intracranial aneurysms and mitral valve prolapse. Subarachnoid haemorrhage or intracerebral bleeding due to rupture of intracranial aneurysm are among the most severe complications of ADPKD and occur in approximately 1 to 2% of patients. Rapid diagnosis and urgent neurosurgical opinion are required. Diagnosis should be suspected early, before complete rupture, in patients with ADPKD with recent and severe headache, or with any transient focal neurological deficit. In cross-sectional studies performed using noninvasive screening methods such as high-resolution CT or magnetic resonance angi- ography, intracranial aneurysms have been found in 7 to 8% of asymptomatic middle-aged patients with ADPKD. The prevalence is higher in those with a family history of intracranial aneurysm. The risk of rupture is largely dependent on aneurysm size. Routine screening by noninvasive methods is not indicated for all asymp- tomatic patients with ADPKD, but it seems reasonable in certain subgroups, in particular those with a family history of intracranial aneurysm or subarachnoid haemorrhage, those who have already bled from an aneurysm (since recurrent aneurysm is possible), and possibly those who are to undergo major elective surgery. In high- risk groups, screening should be repeated every 5 to 10 years since the cerebral vascular disease is progressive. Mitral valve prolapse is discovered in 20% of patients with ADPKD by echocardiography, whereas it is found in only 2 to 3% of the general population. Other cardiac valve abnormalities and occa- sionally artery dissection or aneurysm may also be detected. Other extrarenal abnormalities observed in ADPKD include pes excavatum, colonic diverticula, and abdominal hernias. Pathogenesis Cysts develop only in a few nephrons and only focally, whereas all nephron cells carry the mutated gene. This has been explained by a two-hit phenomenon which postulates that renal tubular (or liver bil- iary) cells that are at the origin of cysts bear first the germinal PKD gene mutation, and then acquire a somatic PKD gene mutation involving the other allele, this event occurring at random in a limited number of cells. This explanation does not exclude other mechanisms. The link be- tween the genetic event(s) and cystic fluid accumulation is not known. The disease has an autosomal dominant mode of inheritance, so that the risk of any child of an affected parent carrying the abnormal gene is one in two, new mutations being rare. Mutations affecting polycystin 1 (from the PKD1 gene on the short arm of chromosome 16) are responsible for 75% of cases in the most recent series, with mu- tations affecting polycystin 2 (from the PKD2 gene on the long arm of chromosome 4) accounting for most of the remainder. Polycystin 1 and polycystin 2 are transmembrane proteins that are able to interact, function together as a nonselective cation channel, and also induce several distinct transduction pathways. The ‘polycystin complex’ may have three different subcellular localizations and associated putative functions: at lateral membranes of the cells (with a role in cell–cell interaction), at the basal pole of the cell (with a role in cell– extracellular matrix interaction), and at the apical primary cilia of the cells (with a role in mechanotransduction of the urinary flux). Treatment—general and symptomatic High fluid intake and regular follow-up of blood pressure and renal function are indicated in all patients with ADPKD. The control of hypertension is an essential part of management, achieved with standard antihypertensive agents. Haematuria should be managed conservatively if possible, although bleeding may sometimes be pro- longed over several days and even weeks. The relief of pain or abdominal discomfort can be difficult. In add- ition to symptomatic treatment, surgical renal cyst decompression should be restricted to very selected cases. Surgery is rarely needed in the management of renal stones. Liver cyst aspirations by needle under CT guidance, fenestration, or resection may be needed when massive involvement gives rise to pain; and in very rare cases such

patients have come to liver transplantation. Kidney infection requires administration of antimicrobials appro- priate for upper urinary tract infection (see Chapter 21.13). In some cases, control of infection is not obtained, most probably because agents penetrate some infected cyst fluids poorly and do not achieve adequate concentration. Lipophilic drugs such as trimethoprim–sulphamethoxazole and fluoroquinolones have the best penetration into cyst fluid. Liver cyst infection also requires antimicrobials and drainage if infection is not controlled. Standard medical management of chronic renal failure is indi- cated, as are renal replacement therapy and kidney transplantation when the patient reaches endstage, the results being similar to those obtained in other renal diseases.

section 21 Disorders of the kidney and urinary tract 5068 Treatment—specific Identification of polycystins and their downstream intracellular dysregulated signalling pathways has provided clues to how the disease develops and thereby to the possibility of specific inter- ventions. Among various molecules, V2 receptor antagonists (tolvaptan), somatostatin analogues (octreotide), and mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus) have been tested and shown promise in animal models. A ran- domized trial of tolvaptan in patients aged 18 to 50 years, with an estimated glomerular filtration rate greater than 60 ml/min and total kidney volume greater than 750 mL, demonstrated a reduced rate of annual increase in total kidney volume (2.8% vs 5.5%), a reduced annual rate of decline of renal function (−3.0 μmol/L vs −4.3 μmol/L), and reduced rate of reaching a composite endpoint comprising measures of clinical progression and rate of kidney function decline (44 vs 50 events per 100 patient-years of follow- up). Patients who took tolvaptan had a higher rate of adverse events related to aquaresis, but a lower frequency of adverse events re- lated to ADPKD. Elevation of serum alanine aminotransferase to more than 2.5 times normal occurred in 4.9% of patients taking tolvaptan (vs 1.2% controls), and the United States Food and Drug Administration has subsequently issued a safety warning about the possibility of irreversible liver injury associated with the use of the drug. In the United Kingdom the National Institute for Health Care and Excellence have recommended Tolvapatan as an option to slow progression of cyst development and renal failure in patients with CKD stages 2 or 3 who have evidence of rapidly progressing disease, subject to the medication being provided at an agreed discount. Clinical trials of octreotide have shown a tendency for reduction in increase in renal size and decline in glomerular filtration rate, but without the reductions reaching statistical significance and with a suggestion that beneficial effects may be attenuated after 2 years. Clinical trials of everolimus and sirolimus have not shown signifi- cant clinical benefit, and these agents have a formidable side effect profile. Genetic counselling The pattern of inheritance of ADPKD means that the offspring of an affected subject each have a 50% risk of having the disease. The dis- ease has a highly variable clinical course, even within a given family. Prenatal diagnosis by gene linkage studies using material derived from chorionic villus sampling has been performed and can be con-sidered if required and if adequate family information is available, but the demand for such prenatal diagnosis has been very low in Western countries. This is explained by the late onset and the vari- able clinical course of the disease, often relatively benign, which cannot yet be predicted by DNA analysis. Ultrasonography may occasionally show renal cysts in the fetus, but late in pregnancy. Obviously, due to the slow and late develop- ment of macrocysts, negative ultrasonography in the fetus (as well as in a child) does not rule out the disease. Autosomal recessive polycystic kidney disease Autosomal recessive polycystic kidney disease (ARPKD) is a rare inherited disease (c.1 in 40 000 individuals), the first manifest- ations of which appear early in childhood. Mutations at a single locus, polycystic kidney and hepatic disease 1 (PKHD1, located on

chromosome 6), are responsible for all typical forms of ARPKD. The PKDH1 gene product, fibrocystin, is a transmembrane protein local- ized to the cell primary cilia. Three clinical features characterize this disease: • Its recessive nature: both heterozygous parents are unaffected, with normal renal ultrasonography; parental consanguinity is found in some families. • Renal cysts derive from the collecting ducts, accounting for the striations in the dilated collecting system seen on MRI. • The renal disease is in most cases associated with congenital hepatic fibrosis: this may be responsible for portal hypertension due to presinusoidal block, or for bacterial angiocholitis due to intrahepatic bile duct dilatation. In children, ARPKD should be differentiated from ADPKD, which can be detected in childhood, even in neonates. Family history and renal ultrasonography in parents are decisive for correct diagnosis. In very rare families with PKD1 disease, renal involvement may be revealed in neonates and may progress to endstage within the first year of life. The diagnosis of ARPKD may be made before birth by ante- natal ultrasonography, showing renal enlargement and increased echogenicity (as well as oligohydramnios). However, prenatal diag- nosis may be uncertain and, since cystic changes occur in well- developed collecting ducts, these are detected only in the second half of pregnancy. When there is huge renal enlargement, pulmonary hypoplasia and respiratory distress may lead to death within hours after birth. With prolonged survival, liver and renal involvement becomes prominent. Gastrointestinal bleeding due to portal hyper- tension may be life-threatening and necessitate surgical portocaval shunt. Systemic hypertension is a frequent finding in the first year of life but, surprisingly, it may regress in subsequent years. Urinary tract infection is common. The rate of progression of renal failure is variable: of those who survive the neonatal period, about 50% reach endstage in childhood, whilst this occurs in adulthood in the remainder. TCF2 mutation; renal cysts and diabetes syndrome (RCAD) Heterozygous mutations in the TCF2 gene encoding hepatocyte nuclear factor (HNF)-1β, a DNA transcription factor, were initially described as one of the main molecular causes of maturity-onset dia- betes of the young (MODY) type 5. It now appears that renal anom- alies are the key feature of HNF1β mutation phenotype and often precede the onset of diabetes. Renal cysts and progressive renal failure are frequent; glomerulocystic kidney disease and renal hypoplasia have been reported. Abnormal liver function tests, hyperuricaemia, hypomagnesaemia, pancreatic hypoplasia, and urogenital malforma- tions have also been related to HNF1β mutations. Other hereditary cystic kidney diseases Renal cysts may be found in other autosomal dominant diseases, such as von Hippel–Lindau disease, tuberous sclerosis, as well as in three recently identified major causes of familial tubulointerstitial nephritis (UMOD, REN, and MUC1 gene mutations) with frequent medullary cysts. Most of these rare condition progress to endstage renal failure. Renal medullary cysts are also found in juvenile nephronophthisis, but not early in the course.

21.12 Renal involvement in genetic disease 5069 Genetic glomerular diseases Glomerular structural diseases In glomerular structural diseases, proteins of podocytes or base- ment membrane are mutated (Table 21.12.3). X-linked Alport’s syndrome Basement membranes of glomeruli may be altered by type IV col- lagen mutations. Six α chains of type IV collagen have been iden- tified so far, with each molecule of type IV collagen being made up of three of these chains, differently associated in various basement membranes. In X-linked Alport’s syndrome, mutations have been identified in the gene encoding the α-5 chain that maps to the long arm of the X chromosome. X-linked Alport’s syndrome is characterized by the association of progressive haematuric hereditary nephritis and bilateral sensorineural hearing loss. Its prevalence is approximately 1 in 5000 individuals. The first renal manifestation is typically visible haematuria, occurring sometimes in the first year of life, recurring during childhood, and followed by permanent

nonvisible haematuria. Proteinuria appears later. A nephrotic syndrome, usually moderate, develops in 30 to 40% of patients. In other cases, moderate protein- uria and nonvisible haematuria are the presenting symptoms in adulthood. By electron microscopy, the basement membrane can be abnormally thickened with splitting of the lamina densa, thinned with focal thickening, or diffusely thin. The disease is progressive, leading to renal failure in all affected males, but the rate of progres- sion is heterogeneous from one family to another, although usually homogeneous within a given family. In some, endstage is reached at or before 30 years of age, sometimes in childhood; in others, renal failure progresses to endstage between the ages of 30 and 60 years. Carrier females of X-linked Alport's syndrome often have slight or intermittent urinary abnormalities. Some may develop impairment of renal function late in life. The hearing defect may lead to severe perceptive deafness, but it is often moderate or slight, only detected by audiometric testing. The hearing loss labels a given family, but is not found in all patients with renal disease. Eye abnormalities are detected in 30 to 40% of cases. These include bilateral anterior lenticonus detected by slit-lamp examination—a pathognomonic abnormality—and perimacular or macular retinal flecks that are seen by fundoscopic examination and do not alter visual acuity. Recurrent corneal erosions occur in some patients. Genetic counselling first requires the correct identification of the mode of inheritance. If X-linked dominant inheritance is docu- mented, affected men will not transmit the disease to their sons, whereas all their daughters will carry the mutant gene; affected women will transmit the mutant gene to 50% of either sons or daughters. DNA analysis may be helpful for genetic counselling in these families. Treatment of hypertension and supportive management of renal failure are indicated in patients with progressive disease. The re- sults of kidney transplantation are similar to those obtained in other renal diseases, but in rare cases antiglomerular basement membrane crescentic glomerulonephritis develops in the graft. It is assumed that this complication is related to alloimmunization to the 'missing antigen' introduced by the transplant. Autosomal Alport's syndromes In the autosomal recessive form, renal disease progresses to endstage before 20 to 30 years of age at a similar rate in both affected men and women. The genes encoding α-3 or α-4 chains are mu- tated. Affected subjects are homozygotes in consanguineous fam- ilies, or compound heterozygotes in other cases. In families with leiomyomatosis, α-5 and α-6 genes, located contiguously on the X chromosome, are both involved in a large deletion. In some families, macrothrombocytopenia is associated with nephritis and hearing defects: mutations involve the MYH9 gene, encoding the nonmuscle myosin heavy chain IIA. Table 21.12.3 Genetic glomerular structural diseases Disease Gene (OMIM) Inheritance Renal phenotype Extrarenal phenotype X linked Alport's syndrome COL4A5 (301050) XL Nonvisible haematuria (constant) ± episodes of visible haematuria; increasing proteinuria ± nephrotic range, progressive renal failure. Early endstage renal disease (ESRD) in most males Sensorineural hearing loss; anterior lenticonus and other eye anomalies Myosin heavy chain 9 (MYH9) MYH9 AD Nonvisible haematuria, proteinuria, progressive renal failure Macrothrombocytopenia Leucocyte inclusions Sensorineural hearing loss Cataract Nail patella syndrome (osteo-onychodysplasia) LMX1B (161200) AD Focal and segmental glomerulosclerosis with specific ultrastructural changes of the glomerular basement membrane, in 30% of patients, may progress to ESRD in some Inconstant. Absence, dysplasia, or hypoplasia of the nails and patella; elbow dysplasia; bilateral iliac horns arising from the anterosuperior iliac crest; eye disease and sensorineural hearing loss possible Congenital nephrotic syndrome of the Finnish type Nephrin AR Massive proteinuria occurs in utero and persists in infancy. Intense therapy needed: nutritional support to compensate for protein loss; prevention of infection and thrombosis;

bilateral nephrectomy; continuous peritoneal dialysis, and finally kidney transplantation None Familial focal segmental glomerulosclerosis Various (see text) AR or AD Progressive proteinuria, sometimes nephrotic. May progress to ESRD None AD, autosomal dominant; AR, autosomal recessive; XR, X-linked.

section 21 Disorders of the kidney and urinary tract 5070 Benign familial haematuria This condition is characterized by isolated nonvisible haema- turia, without proteinuria or progression to renal failure, in both men and women. Renal biopsy usually shows a thin glomerular basement membrane (hence the alternative name thin basement membrane nephropathy) and immunofluorescence studies are negative. The mode of transmission is compatible with auto- somal dominant inheritance of mutations involving the α-3 or α-4 chain gene. Familial focal segmental glomerulosclerosis Familial focal segmental glomerulosclerosis with either autosomal dominant or autosomal recessive inheritance has been well charac- terized. Mutation of the NPHS2 gene, which encodes podocin, and mutations of PLCE may cause recessive steroid-resistant nephrotic syndrome in some families, which can be of early or late onset. Mutations in ACTN4, which encodes α-actinin-4, mutations of TRPC6, and mutations of INF2 (which encodes formin) may cause autosomal dominant focal segmental glomerulosclerosis. All these proteins are synthesized and secreted by the podocytes, and interact and regulate plasticity and slit diaphragm permselectivity with other podocyte proteins. Mutations (especially podocin mu- tations) may be detected in some cases of sporadic steroid-resistant nephrotic syndrome. Nephrin is localized at the slit diaphragm be- tween podocyte foot processes (which are both absent in affected subjects), and plays a key role in the normal glomerular filtration barrier. Mutations of nephrin are responsible for autosomal reces- sive congenital nephrotic syndrome. Familial IgA nephropathy For most types of other primary glomerulonephritis, familial cases have been anecdotally reported. The most frequent form, albeit rare, is probably familial IgA nephropathy, either primary (Berger’s dis- ease) or associated with Henoch–Schönlein purpura. Metabolic diseases with glomerular involvement In metabolic diseases with glomerular involvement, a defect in an enzyme or its cofactor leads to accumulation or deficiency of a specific metabolite. Fabry disease’s, mitochondrial cytopathy, lecithin-cholesterol acyl transferase (LCAT) deficiency, hepatorenal glycogenosis (glucose-6-phosphatase deficiency), and glycogen storage disease type I are the most important diseases in this group (Table 21.12.4). Fabry’s disease Fabry’s disease, a rare X-linked lysosomal storage disease, results from α-galactosidase A deficiency. Glycosphingolipid deposition mainly occurs in the cardiovascular and renal system. Hemizygotes males are more severely affected than heterozygote females. The first manifestations are painful acroparaesthesias, appearing in child- hood and often prevented by administration of carbamazepine or phenytoin. Angiokeratomas, anhidrosis, and corneal deposits de- velop subsequently. Ischaemic cerebrovascular complications, car- diac valve abnormalities, myocardial deposition of glycolipids, and coronary events are the most severe manifestations, along with renal involvement. In the kidney, glycolipid deposition involves glomerular epithe- lial cells, tubular cells, and endothelial and smooth muscle cells of intrarenal arteries. The latter changes are responsible for progressive renal ischaemia. Renal disease is revealed by proteinuria at around 20 years, and then progresses to endstage between 40 and 60 years of age, necessitating regular dialysis and/or kidney transplantation. Glycolipid deposition does not recur in the renal graft that contains normal α-galactosidase activity. Diagnosis is based on symptoms, familial history, measurement of α galactosidase activity in leucocytes, demonstration of typical inclusions on a tissue biopsy, and genetic analysis. Two different re- combinant enzyme treatments (agalsidase α and agalsidase β) have been available since 2001.

Enzyme replacement therapy promotes Table 21.12.4 Genetic glomerular metabolic diseases Disease Gene (OMIM) Inheritance Renal phenotype Extrarenal phenotype Fabry's disease GLA (301500) XL Mostly in men: proteinuria, progressive kidney failure; sometimes tubular dysfunction (polyuria, Fanconi's syndrome) and renal parapyelic cysts. Glycolipids accumulation observed on light and electron microscopy Pain (acromelalgia), skin (angiokeratomas, anhidrosis), eye (cornea verticillata), heart (left ventricular hypertrophy, conduction anomalies, valve anomalies, angina), strokes (hearing loss, ataxia, vascular dementia) Mitochondrial cytopathy, MIDD type MT-TL1 (520000) Mitochondrial Proteinuria, progressive renal failure (focal segmental glomerular sclerosis, tubulointerstitial nephritis) Sensorineural hearing loss and diabetes in adults (seek for maternal inheritance); pigmentary retinopathy, ptosis, cardiomyopathy, myopathy, neuropsychiatric symptoms Lecithin-cholesterol acyl transferase (LCAT) deficiency LCAT (245900) AR Lipid accumulation occurs in glomerular mesangial cells and progresses to endstage renal disease. Lipid deposition recurs slowly in kidney transplants Lipid accumulation occurs in the eyes (causing corneal deposits), erythrocyte membranes (leading to low-grade haemolytic anaemia), arterial walls (contributing to premature atherosclerosis) Hepatorenal glycogenosis (glucose-6-phosphatase deficiency; glycogen storage disease type I; von Gierke) G6PC (type a 232200) SLC37A4 (type b 232220) AR Early enlarged kidneys Late glomerular hyperfiltration proteinuria, progressive renal failure Early hypoglycaemia, intolerance to fasting, hepatomegaly, growth retardation, osteopenia, round face, platelet ± neutrophil dysfunction, enteropathy Late hepatic adenomas and carcinomas AR, autosomal recessive; XR, X-linked.

 cell clearance of substrate and improves some clinical parameters (heart, kidney damage, pain, quality of life). However, there is no proven efficacy to date on central nervous system lesions, on car- diac morbidity and mortality, nor on renal damage beyond a certain stage (proteinuria >1 g/day and/or estimated glomerular filtration rate <60 ml/min per 1.73 m2). Genetic diseases with renal tumours Renal cell carcinomas occur in both sporadic and heritable forms. Four major autosomal dominantly inherited renal cell carcinoma syndromes have been identified: von Hippel–Lindau syndrome, Birt–Hogg–Dubé syndrome, hereditary leiomyomatosis and renal cell cancer, and hereditary papillary renal cancer (Table 21.12.5). Heritable renal cell carcinoma should be suspected in various situ- ations: young age, bilateral lesions, positive family history, and extrarenal phenotype. The VHL gene mutated in von Hippel–Lindau syndrome is a tu- mour suppressor gene: two mutations ('two-hit' phenomenon) are required to trigger tumour formation, the first one being germinal (inherited) and the second one somatic. Renal cysts and bilateral multifocal renal cell carcinomas are found in 70% of the patients. Carcinomas are often asymptomatic, should be screened for regularly (Fig. 21.12.2), and occur at a mean age of 45 years. Nephron-sparing surgery (tumourectomy) or percutaneous radiological interventions (radiofrequency ablation or cryoablation) are advocated when tech- nically feasible. Early treatment of multiple and recurrent renal cell carcinomas prevents metastatic disease, spares nephrons, and is asso- ciated with a significant improvement of renal prognosis. Angiomyolipoma, a benign and frequent sporadic renal tumour, is the most typical renal lesion encountered in tuberous sclerosis, where it is usually multiple, bilateral, and associated with extrarenal manifestations. Two genes are identified in tuberous sclerosis: TSC1 on chromosome 9q, encoding hamartin, and TSC2 on chromo- some 16p, encoding tuberin. By ultrasonography, angiomyolipomas are hyperechogenic, and by CT they are characterized by their high fat content (Fig. 21.12.3). Bleeding is the main complication of renal angiomyolipoma. Multiple angiomyolipomas may also severely reduce renal mass and lead to renal failure. The develop-

ment of segmental glomerulosclerosis may accelerate the progres- sion to endstage. Renal cysts may also be found in TSC2 forms, and the incidence of renal cell carcinoma is slightly higher than in the general population. Everolimus inhibits the mTOR complex 1 pathway and reduces the size of angiomyolipomas in patients with tuberous sclerosis; its use is approved for asymptomatic, growing, Fig. 21.12.2 CT of the kidneys in a patient with von Hippel–Lindau disease. In the right kidney, a solid tumour is found as well as cystic changes. In the left kidney, a voluminous multilocular tumour is detected with thick walls, corresponding to renal clear cell carcinoma, associated with other cystic lesions. Table 21.12.5 Genetic diseases causing renal tumours Disease Gene (OMIM) Inheritance Renal phenotype Extrarenal phenotype Von Hippel–Lindau disease VHL (193300) AD Renal cysts and cancers (clear cells renal carcinomas) Haemangioblastoma of the cerebellum, brain stem, spinal cord, and retina; phaeochromocytoma; pancreatic cysts and carcinoma; epididymal cystadenoma Birt–Hogg–Dubé syndrome BHD (135150) AD Hybrid (chromophobe, ococytoma, renal cell carcinoma) Fibrofolliculomas, pulmonary cysts, pneumothorax, colorectal polyps Hereditary leiomyomatosis and renal cell cancer (HLRCC) FH (150800) AD Papillary carcinoma, type 2 (bilateral, multifocal) Skin leiomyoma, uterine leiomyoma Hereditary papillary renal cancer (HPRC) MET (179755) AD Papillary carcinoma, type 1 (bilateral, multifocal) None Tuberous sclerosis STB1 (191100) STB2 (613254) AD Multiple and bilateral angiomyolipomas and renal cysts; focal and segmental glomerulosclerosis Epilepsy, intellectual disability (central nervous system cortical tubers); astrocytomas; retinal hamartomas; skin lesions (facial angiofibromas, hypopigmented spots, Koenen tumours, café-au-lait spots, shagreen patch); cardiac rhabdomyoma; in women, pulmonary lymphangiomyomatosis AD, autosomal dominant.

section 21 Disorders of the kidney and urinary tract 5072 TSC-related angiomyolipomas greater than 3 cm in diameter. Selected angiomyolipomas may also be treated by renal selective embolization, surgical tumorectomy, or microablative techniques such as radiofrequency ablation or cryoablation. Congenital anomalies of the kidney and urinary tract More than 20 single gene mutations may result in a wide range of congenital anomalies of the kidney and urinary tract, including renal agenesis, renal hypodysplasia, multicystic dysplastic kidney, hydronephrosis, ureteropelvic junction obstruction, megaureter, ureter duplex, vesicoureteral reflux, and posterior urethral valves. These anomalies may be associated with extrarenal symptoms. Congenital anomalies account for 40 to 50% of children with chronic kidney disease: Table 21.12.6 describes on the four main causes. Genetic disorders with nephrolithiasis Pertinent clinical data on these disorders are summarized in Table 21.12.7. Additional information can be found in Chapters 21.14, 21.15, and 21.16. Other genetic diseases with kidney involvement Cystinosis Cystinosis (which is to be clearly distinguished from cystinuria that is due to defective reabsorption of cystine in the proximal tubule; see Chapter 21.14) is a rare (1 in 200 000 live-born babies), autosomal recessive condition that results from defective carrier-mediated transport of cystine through the lysosomal membrane due to mu- tations in the gene encoding cystinosin (CTNS). The diagnosis is based on the findings of cystine crystals in tissues, such as the eyes, and on the elevated cystine content in leucocytes. The clinical manifestations are due to progressive intralysosomal accumulation of cystine. In the infantile form, the first symptoms are related to the clinical consequences of Fanconi’s syndrome (salt and water depletion, hypokalaemia, acidosis, and rickets) appearing be- fore 6 months of age. Renal failure develops later, reaching endstage generally before 12 years. In addition to symptomatic management, cysteamine has proved to be effective in cystinosis. It accumulates within lysosomes, pro- motes cystine outflow, and thus reduces tissue cystine content. Administration of this drug should be started as soon as the diag- nosis is made. It may

slow the rate of progression of renal failure and prevent most extrarenal complications. However, despite recent progress, tolerance of the drug is not good because of its offensive taste and odour, so compliance may be poor. Topical cysteamine prevents corneal crystal deposition. Fig. 21.12.3 Multiple bilateral renal angiomyolipomas in a patient with tuberous sclerosis (CT scan). Note the voluminous angiomyolipoma (with high content of fat that is black) at the periphery of the right kidney. Table 21.12.6 Congenital anomalies of the kidney and urinary tract Disease Gene (OMIM) Inheritance Renal phenotype Extrarenal phenotype HNF1β disease (renal cysts and diabetes syndrome; MODY type 5 diabetes) TCF2 (137920) AD Renal cysts, renal dysplasia, renal hypoplasia, single kidney, horseshoe kidney Diabetes mellitus (MODY type 5) Hyperuricaemia, hypomagnesaemia, elevated SGOT, SGPT Renal coloboma syndrome PAX2 (120330) AD Renal hypoplasia, vesicoureteral reflux, oligomeganephronia Optic nerve coloboma Branchio-oto- renal (BOR) syndrome EYA1 (113650) SIX1 (610896) AD Hypoplasia, dysplasia, aplasia (uni- or bilateral), Various collecting system anomalies Laterocervical fistulas or cysts, outer, middle and inner ear anomalies Bardet–Biedl syndrome BBS1–17 (209900) AR ± oligogenic Hypertension, tubular dysfunction (diabetes insipidus, acidosis), abnormal calyces, communicating cysts, fetal lobulation, interstitial nephritis, glomerular scarring, renal failure Retinal degeneration, polydactyly, obesity, short stature, mental retardation, hypogonadism AD, autosomal dominant; AR, autosomal recessive.

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tuberous sclerosis complex. Am J Med Genet Semin Med Genet, 178, 338–47. Joly D, et al. (2011). Progress in nephron sparing therapy for renal cell carcinoma and von Hippel-Lindau disease. JURO, 185, 2056–60. Genetic diseases with urolithiasis Cochat P, Rumsby G (2013). Primary hyperoxaluria. N Engl J Med, 369, 649–58. Genetic diseases with kidney involvement Hildebrandt F (2010). Genetic kidney diseases. Lancet, 375, 1287–95. Joly D, Béroud C, Grünfeld J-P (2015). Rare inherited disorders with renal involvement-approach to the patient. Kidney Int, 87, 901–8. Remuzzi G, et al. (2014). Rare inherited kidney diseases: challenges, opportunities, and perspectives. Lancet, 383, 1844–59. Table 21.12.7 The main inherited disorders associated with nephrolithiasis Disease Mode of transmission Type of stone Chronic renal failure Specific treatment Cystinuria AR Cystine No Urine alkalinization d-penicillamine or other chelators Idiopathic hypercalciuria Unknown Calcium No Diet (normal sodium and protein intake) Thiazide Primary hyperoxaluria type I AR Monohydrated calcium Yes (nephrocalcinosis) Vitamin B6 Oxalate Liver transplantation Dent's disease XR Calcium Yes (nephrocalcinosis) Distal tubular acidosis AR/AD Calcium No Potassium citrate or bicarbonate HPRT deficiency (Lesch–Nyhan syndrome) XR Uric acid Yes Urine alkalinization Allopurinol APRT deficiency AR 2,8-dihydroxyadenine Yes (rarely) Allopurinol Xanthinuria AR Xanthine No AD, autosomal dominant; APRT, adenine phosphoribosyl transferase; AR, autosomal recessive; HPRT, hypoxanthine-guanine phosphoribosyl transferase; XR, X-linked.

ESSENTIALS Urinary tract infection (UTI) is a common condition, accounting for 1 to 3% of all primary care consultations in the United Kingdom. It affects patients of both sexes and all ages. The commonest or- ganism causing uncomplicated community-acquired bacterial UTI is Escherichia coli. Aetiology and pathogenesis The occurrence and course of a UTI is influenced by the integrity of the host defence and by bacterial virulence factors. Disruption of the highly specialized transitional cell epithelium which lines the urinary tract, incomplete bladder emptying, anatomical abnormalities, and the presence of a foreign body, such as a urinary catheter, can all con- tribute to disruption of the host defence and increase the likelihood of infection. Sexual intercourse and use of spermicides increase the risk, and genetic factors influence the susceptibility of some people. Bacterial characteristics that determine their ability to cause infection include specific mechanisms to adhere to the uroepithelium ('pili' or 'fimbriae' in the case of certain E. coli), or adaptations allowing them to colonize foreign surfaces, such as a urinary catheter (proteus), and subsequently cause infection. Clinical features and diagnosis Presentation—cystitis commonly presents with some combination of dysuria, urgency, frequency, polyuria, suprapubic tenderness, and haematuria. Patients with pyelonephritis often have loin pain and other systemic symptoms, with or without symptoms of cystitis. Asymptomatic infection is common, especially in older people, but it is not justified to send a urine sample from an asymptomatic patient for culture, with the notable exceptions of pregnant women, when treatment is mandatory, and prior to invasive urological surgery, when treatment prior to surgery can reduce the risk of postoperative sepsis. Diagnosis—acute uncomplicated UTI can often be diagnosed on symptoms alone, with urinalysis increasing diagnostic accuracy. Submission of a sample for microbiological testing is unnecessary in most cases (exceptions to this rule include pregnancy, recurrent infection, and those patients with abnormal host defences). Current United Kingdom and European guidelines on the level of bacterial counts required to diagnose 'significant' infection are variable and should not be used as the sole determinant of whether antibiotic treatment should be initiated. Differential diagnoses ('culture-negative syndromes')—these include (1) chlamydial infection, which must be identified and treated to avoid long-term complications such as infertility; also (2) urethral syndrome and (3) painful bladder syndrome (interstitial cystitis), which

significantly affect a patient’s quality of life and for which treat- ment is often unsuccessful. Investigation—beyond microbiological testing, further investiga- tion of women with uncomplicated UTI is seldom justified. In men, and those women with features indicating complicated infection, in- vestigation for an underlying cause should be considered: diabetes must be excluded, and anatomical or functional abnormality of the urinary tract sought, as appropriate, by imaging, cystoscopy, and urinary flow studies. Management Antibiotics—trimethoprim and nitrofurantoin remain the first choice for community-acquired UTI in the United Kingdom. Complicated UTI is caused by a wider spectrum of organisms, and recommenda- tions for treatment differ. Guidelines on specific antibiotic treatment and duration of treatment are available, but with increasing antibiotic resistance (including of E. coli to trimethoprim), local microbiological advice should be taken into account. Prevention of recurrent uncomplicated UTI—many clinicians advise patients with such recurrence to take measures to improve perineal hygiene, to empty the bladder after sexual intercourse, to maintain a high fluid intake, and (if vesicoureteric reflux is suspected) to practise double voiding, but the evidence that these measures are effective is weak. Long-term antibiotic prophylaxis reduces the rate of recur- rent UTI, but at the risk of adverse effects. Nightly, thrice weekly, and postcoital prophylaxis have all been shown to be of benefit, but there is no evidence to support the use of rotating antibiotic prophylaxis. Cranberry extract and methenamine hippurate are effective in some patients and have the advantage of not increasing the risk of anti- biotic resistance. Oestrogens are not recommended for the routine prevention of recurrent infection in postmenopausal women, but may be of benefit in those with marked atrophic vaginitis. 21.13 Urinary tract infection Charles Tomson and Neil Sheerin

21.13 Urinary tract infection 5075 Complicated urinary tract infections Complicated UTIs are those occurring in a patient with abnormal host defences. It is uncommon for any man with an anatomically normal urinary tract to suffer a UTI. Urethral catheterization—UTI occurs after 2% of in/out urethral catheterizations and after 10 to 30% of 5-day indwelling catheter- ization, and is nearly inevitable in patients with long-term indwelling catheters. This is an important cause of hospital-acquired infec- tion, significantly increasing the risk of Gram-negative septicaemia and mortality. However, management of patients unable to empty their bladder fully for reasons such as prostatic outflow obstruction or neurogenic bladder dysfunction because of spinal cord injury is often difficult without medium- or long-term urinary catheterization. Use of prophylactic antibiotics to cover short-term catheter insertion may be justified, but this is not the case in patients with long-term catheters, although regular bladder washouts and methenamine may be of some benefit. Treatment of asymptomatic bacteriuria in patients with anatomically abnormal urinary tracts or with indwelling urinary catheters is unjustified and likely only to lead to the emer- gence of antibiotic-resistant urinary infection. Clean, intermittent self-catheterization should be considered as an alternative where possible. Urinary tract stones—these are an important cause of recurrent and relapsing UTIs that are difficult or impossible to treat with antibiotic therapy alone, repeated courses of which often encourage the de- velopment of resistant organisms. Removal of stones is often difficult and requires repeated interventions. Identification of the stone type and prevention of formation of further stones is an important part of any treatment plan. Anatomically abnormal kidneys—inherited renal abnormalities such as polycystic kidneys are often complicated by UTI, which can be difficult to treat if the infection involves a cyst. Renal transplant recipients are at an increased risk of UTI due to a variety of factors, including the anatomy of the transplant kidney, postoperative cath- eterization, and immunosuppressive medication. Unusual viral or- ganisms such as polyoma (BK) virus may cause infection in this group of patients. Vesicoureteric reflux—the

normal bladder prevents reflux of urine into the ureters during micturition. Congenital abnormalities of the vesicoureteric junction can allow this to occur, as can acquired ab- normalities such as bladder outflow obstruction, which disrupts normal host defence against ascending infection and thus makes children (particularly girls) more prone to ascending UTI. Cortical defects (‘scars’) in the upper and lower poles of the kidneys are fre- quently found in such children. These may be caused by ascending infection causing acute pyelonephritis, but similar appearances can occur in the absence of UTI and are likely due to renal dysplasia, in- herited along with abnormal insertion of the ureters into the bladder. Progressive kidney failure may occur in such patients, but it is more likely that this is due to the late effects of renal dysplasia and con- genital reduction in renal mass, rather than to the effects of scarring caused by ascending infection. Clinical trials comparing long-term prophylactic antibiotics for the first 5 years of life versus surgical ur- eteric reimplantation have shown a similar incidence of symptom- atic UTI in both treatment groups; whether either treatment reduces the risk of the development of new scars or of progressive kidney failure remains uncertain. Pregnancy—there is a significantly increased risk of acute pyelonephritis in pregnant women with untreated bacteriuria, many of whom will be asymptomatic. Late pyelonephritis is associated with an increased incidence of preterm delivery and low birth weight, hence the need in pregnancy to screen for and treat UTI promptly with antibiotics. Ascending UTI is rarely complicated by unusual conditions such as acute papillary necrosis or perinephric abscess. These can lead to destruction of renal parenchymal tissue and chronic kidney dis- ease, usually in the context of abnormal host defence such as dia- betes or urinary tract obstruction. Malakoplakia is an extremely rare complication of bacterial UTI, characterized by destructive tu- mour-like granulomatous infiltrates in the urinary bladder, kidneys, and (occasionally) other organs. Other causes of UTI may need to be considered depending on the patient’s ethnic background and medical and travel history (e.g. fungal infections, tuberculosis, and schistosomiasis). Introduction ‘Urinary tract infection’ (UTI) refers to bacterial, viral, or fungal in- fection of the kidneys, renal pelvis, ureters, or bladder. Infections primarily involving the urethra are nearly always sexually acquired and are dealt with elsewhere (see Section 9). ‘Pyelonephritis’ refers to infection primarily involving the kidneys and collecting sys- tems. ‘Cystitis’ refers to infections localized to the urinary bladder. ‘Recurrent’ UTIs are due to repeated reinfection, whether by similar organisms on each occasion or by different species; ‘relapsing’ and ‘persistent’ infections are due to the continued presence of the same organism, suppressed or not suppressed during antibiotic therapy. ‘Uncomplicated’ UTIs occur in an anatomically and functionally normal urinary tract; ‘complicated’ infection refers to all infections occurring in patients either with impaired host defence (e.g. dia- betes), with abnormal urinary tract function (e.g. pregnancy), or ab- normal urinary tract anatomy (e.g. urinary tract obstruction). Infection of the urinary tract is important for different reasons in different age groups. In infants and children, ascending infection is thought to be a preventable cause of renal parenchymal scarring and eventual renal failure, although it is controversial how frequently this occurs. In adult women, recurrent lower UTI (‘cystitis’) is a common cause of time off work. In all age groups, persistent or relapsing infec- tion is an important indicator of abnormal host defences, usually due to abnormal anatomy or function of the urinary tract, and may re- sult in irreversible renal damage unless the underlying cause is dealt with. UTI are the cause of over 50% of Gram-negative septicaemic episodes. In older people, nonspecific symptoms including toxic confusional states are often due to occult UTI. Epidemiology Symptomatic bacterial UTI is one of the commonest bacterial in- fections. Around 1% of boys and 3% of girls will develop a UTI during childhood, and 50% of women will be treated for at least one UTI during their lifetime, with recurrent infections in a signifi- cant minority. UTI is rare in men until

after the age of 60, when

section 21 Disorders of the kidney and urinary tract 5076 the rising prevalence of impaired bladder emptying leads to an in- creased incidence of infection. Asymptomatic bacteriuria is found in about 10% of elderly men and in 20% of elderly women. UTI is one of the commonest bacterial infections managed in primary care, and is the cause of 1 to 3% of all primary care consultations in the United Kingdom. UTI is responsible for over 25% of all community- acquired bacteraemias, more than any other source of infection. The Nosocomial Infection National Surveillance System reported that in England (2011), 17.2% of all healthcare-associated infections were due to UTI, and 7.5% of hospital-acquired bacteraemias were due to catheter-associated UTI. Aetiology The commonest causative organisms in uncomplicated bacterial UTI are Gram-negative gut organisms, particularly Escherichia coli (Box 21.13.1). This reflects the fact that most infections reach the urinary tract via the urethra from the perineum. However, as dis- cussed later, only some subtypes of E. coli and only some of the other species of gut organisms have the necessary virulence characteristics to enable infection of the normal urinary tract. E. coli is the third most common organism causing hospital-acquired bacteraemia. Complicated UTIs are caused by a broader spectrum of bacteria, including Gram-positive in addition to Gram-negative organisms and those with multiple resistance to antibiotics. Pathophysiology The occurrence and course of UTIs are influenced by the integrity of the host defence and bacterial virulence factors. Host defence Most UTIs are acquired by ascent of the infecting organism up the urethra; only a very few result from haematogenous spread or—even less commonly—from vesicoenteric fistulas. The renal pelvis, ure- ters, bladder, and urethra possess a highly specialized transitional cell epithelium, which normally maintains complete impermeability to all components of urine, including toxins and water. This is main- tained by tight junctions between the surface layers of epithelial cells, with a very high transepithelial electrical resistance. In the bladder, this impermeability has to be maintained despite repeated large changes in surface area as the bladder fills and empties. This is maintained by unfolding and refolding of the large, highly folded ‘umbrella’ cells that form the uppermost layer of the epithelium, to- gether with insertion and endocytosis of vesicles, ready-lined with uroplakin, a hexagonal transmembrane protein found only on the surface of umbrella cells. Ascending infection takes place in a series of steps, at each of which defective host defence increases the chance of successful es- tablishment of infection (Fig. 21.13.1). Frequency and completeness of bladder emptying For an ascending infection to become established in the bladder, the number of organisms needs to reach a critical mass. The chance of this happening is reduced by increased urine flow rate, causing dilution of organisms within the bladder, and by frequent voiding, which also flushes the urethra and helps to prevent ascent of or- ganisms into the bladder. This is termed ‘hydrokinetic’ defence. Habitual infrequent voiding is thought to be a risk factor for re- current UTIs for this reason. Patients with recurrent UTIs are rou- tinely advised to increase fluid intake and frequency of voiding, and some women report that a high fluid intake alone is enough to clear symptomatic infection. Incomplete voiding, which may be present in both sexes and is not necessarily due to outflow obstruction (Box 21.13.2), is an important cause of increased susceptibility to urine infection. Vesicoureteric reflux During normal micturition, urine is expelled into the urethra while retrograde flow (‘reflux’) of urine into the ureters is prevented be- cause muscular contraction of the bladder wall results in closure of the vesicoureteric junctions. Reflux of urine into the ureters can occur if this mechanism is defective, followed by return to the Box 21.13.1 Organisms commonly causing uncomplicated UTI • Escherichia coli • Klebsiella pneumoniae • Proteus • Pseudomonas • Enterococcus • Staphylococcus saprophyticus (in sexually

active females) Entry into renal parenchyma

- immature compound calyces
- high pressure Rectum Vagina Urethra Bladder Ureter Colonization by uropathogenic bacteria
- recent antibiotic use Colonization of vaginal and periurethral mucosa by uropathogens
- ABO blood group non-secretor status
- recent wide-spectrum antibiotic use
- oestrogen deficiency
- spermicide use
- poor perineal hygiene Urethral ascent
- sexual intercourse
- urethral catheterization Adherence to uroepithelium
- non-secretor status
- P1 blood group Decreased washout
- impaired bladder emptying
- neurogenic
- outflow obstruction
- detrusor failure Abnormal local mucosal immune response Vesicoureteric reflux
- developmentally abnormal vesicoureteric junction
- obstructive uropathy
- pregnancy
- neurogenic bladder Impaired clearance
- obstruction
- stones Fig. 21.13.1 Mechanisms allowing ascent of infection up the urinary tract.

21.13 Urinary tract infection 5077 bladder once bladder contraction has finished. The most common cause of reflux is abnormal insertion of the ureters into the bladder, which occurs as a relatively frequent developmental anomaly. The other major cause is abnormally high intravesical pressure, for ex- ample, in high-pressure chronic retention of urine due to bladder outflow obstruction, or in neurogenic bladder in patients with par- tial spinal cord lesions. Whatever the cause, reflux of urine results in failure to expel all bladder urine during micturition and therefore significantly impairs host defence against infection, as well as being associated with a greatly increased risk of infection ascending to the kidneys and causing acute pyelonephritis. Vesicoureteric reflux is frequently found in children with UTIs. The question of whether as- cending infection is a cause of renal damage in children with reflux is discussed later in this chapter. Foreign bodies, stones, and privileged sites The presence of a foreign body, such as a urinary catheter or ureteric stent, or a stone within the urinary tract, creates a protected site where uropathogenic organisms can adhere and multiply, relatively protected from both hydrokinetic and mucosal defence mechan- isms. In this situation, it is often impossible to eradicate urine in- fection unless the foreign body or stone is removed, and prolonged use of antibiotics often results in the acquisition of resistance by the infecting organism. Urinary infection is nearly inevitable after a few weeks of bladder catheterization. Other ‘privileged’ sites in- clude renal cysts (as in polycystic kidney disease, discussed later) and bladder diverticula. Sexual activity Many women first experience acute cystitis shortly after becoming sexually active. Most women have transient bacteriuria after sexual intercourse, which develops into symptomatic cystitis only in a mi- nority.

In case–control studies of young women, the risk of UTI was associated with vaginal intercourse, and increased further by condom use. These findings are explained by the mechanical effect of intercourse encouraging ascent of organisms up the urethra, an effect that may be exacerbated by condom use, particularly without lubri- cants. The risk of UTI is also increased by a change in sexual partner, which may reflect male-to-female transmission of uropathogens. Use of spermicides as an adjunct to barrier contraceptive methods is also associated with an increased rate of periurethral colonization with E. coli and other uropathogens and with an increased risk of symptomatic UTI, probably because the active component in sper- micides (nonoxynol-9) is bactericidal against lactobacilli. The pro- tective effect of micturition soon after intercourse, based on the supposition that washout of recently introduced bacteria will pre- vent establishment of infection, remains unproven. Vaginal and periurethral flora Vaginal secretions are normally colonized by lactobacilli that ap- pear to protect against colonization by uropathogenic bacteria such as E. coli. The mechanism of this protection is uncertain, but may in part be related to the maintenance of an acidic pH, which sup- presses growth of some uropathogenic bacteria. Suppression of this normal vaginal colonization by antibiotic treatment or by spermi- cide use increases the risk of colonization of the periurethral mucosa by uropathogenic bacteria and subsequent ascending UTI. In add- ition, atrophic vaginitis caused by oestrogen deficiency is associated with the absence of lactobacillus colonization, which may be part of the reason for the increased risk of UTI in postmenopausal women. Genetic factors In laboratory studies, adherence of E. coli to both vaginal and buccal cells is greater in cells taken from women with recurrent UTIs than in cells from healthy controls, and women with recurrent UTIs more frequently have gut colonization by uropathogenic strains of E. coli, suggesting that they experience more frequent UTIs because they are more susceptible to colonization of the periurethral area by uropathogenic bacteria. It appears that this difference in suscepti- bility to colonization and infection, especially in patients in whom there is no other defect of host defence (such as vesicoureteric re- flux), is due to genetically determined differences in the extracellular antigens to which bacteria adhere, in particular in the expression of blood group antigens. The density of glycosphingolipids is higher in patients with the P1 blood group than those with the P2 blood group, and the P1 blood group is a risk factor for acute pyelonephritis among girls without vesicoureteric reflux. Expression of the large oligosaccharide A, B, H blood-group antigens on the cell surface partially or completely ob- scures the smaller glycosphingolipids, preventing them from being bound by type P fimbriae, which is why women with the secretor phenotype, in which these antigens are both expressed on the cell surface and secreted, are less prone to most E. coli infections than nonsecretors. Nonsecretors also have an increased inflammatory re- sponse (fever and acute-phase response) to urinary infection com- pared with secretors, and nonsecretors are over-represented among patients with urographic evidence of reflux nephropathy. However, some E. coli strains only bind to cells from subjects who are secretor- positive blood group A. Local immunity Another aspect of host defence is the local production of antimicro- bial peptides, secreted by uroepithelial cells into the urine, and the secretion of IgA into the urine. However, there is little convincing evidence that impaired local IgA secretion is responsible for in- creased susceptibility to UTI. Patients with defects in systemic im- munity, whether cellular or humoral, do not appear to be at a greatly increased risk of UTI; the risk of UTI with AIDS is only increased in men practising unprotected anal intercourse. Bacterial virulence factors The ability of a bacterium to colonize the gut and periurethral mucosa, and subsequently to adhere to the uroepithelium, is a major determinant of its ability to cause clinical infection, particularly if other host defences are intact. This ability to adhere is governed by a specific interaction between bacterial adhesins, located on the tips of thin filaments (‘pili’ or

‘fimbriae’), with genetically determined Box 21.13.2 Some causes of incomplete bladder emptying • Bladder outflow obstruction: — Benign prostatic hypertrophy — Prostate cancer — Strictures—bladder neck, urethral — Uterine prolapse • Detrusor underactivity • Abnormal bladder innervation: — Spinal cord injury — Autonomic neuropathy (e.g. diabetes)

section 21 Disorders of the kidney and urinary tract 5078 glycoproteins on the cell surface of the host cell. Type 1 fimbriae bind to mannose-containing glycoproteins (uroplakins) that are present on the surface of uroepithelial cells, but also to Tamm– Horsfall protein, which is present in urine and can competitively inhibit binding of bacteria to cell surface glycoproteins. Type P pili bind the α-galactosyl-1,4-β-galactose disaccharide sequence pre- sent in some glycoproteins and glycosphingolipids, including the human P blood-group antigen system, and also on the cell surface of uroepithelial cells as well as red cells. Some uropathogens are particularly adapted to colonizing for- eign surfaces, particularly those coated by biofilm or mucin; for example, proteus are able to transform into a swarming phenotype with massive flagellas, organize into rafts, and move very rapidly against the flow of urine—they are therefore important causes of in- fection in patients with indwelling urinary catheters and those with ileal conduits. Staphylococcus saprophyticus, an important cause of UTI in sexually active young women, is probably better able to cause UTI than S. aureus or S. epidermidis because of its possession of a lactosamine adhesin, permitting adherence to uroepithelial cells. Following adherence, fimbriae appear to retract, drawing the or- ganism closer to the surface of the uroepithelial cell. Adherence is followed by apoptosis, exfoliation, and excretion of infected super- ficial cells and replacement by less differentiated cells, a process that may also contribute to host defence. Some bacteria may also intern- alize into urothelial cells, allowing persistence within the urinary tract and occupation of a site inaccessible to water-soluble anti- biotics. Uropathogenic bacteria also possess other virulence factors including toxin production, resistance to complement-mediated lysis, and metal ion-chelating proteins. Clinical features of UTI Cystitis The commonest presentation of UTIs is with ‘cystitis’, a symptom complex associated with lower UTI in which many of the symptoms are directly attributable to increased bladder irritability caused by local infection, without systemic symptoms. Typical symptoms— not all of which are specific for lower UTI—are listed in Box 21.13.3. Dysuria may be due to urethritis or vaginitis, but these are usually not associated with urinary frequency, and may be associated with vaginal discharge or itching and with specific findings on vaginal examination. There is considerable overlap between the symptoms of UTI, idiopathic overactive bladder (dysuria and haematuria are uncommon), painful bladder syndrome and chemical, drug or radi- ation induced cystitis. Asymptomatic bacteriuria By definition, this is an incidental finding in patients whose urine is cultured despite the absence of urinary tract symptoms. It is seldom justified to send a urine sample from an asymptomatic patient for cul- ture, so this diagnosis should only rarely be made in clinical practice. Two important exceptions are during pregnancy and prior to invasive urological surgery (discussed later). Elderly patients with asymptom- atic bacteriuria are also at increased risk of death, but this is probably because bacteriuria is a marker of poorer general health: antibacterial treatment has not been shown to improve survival in this situation. Acute pyelonephritis The term ‘acute pyelonephritis’ denotes infection within the renal pelvis, with or without active infection within the renal paren- chyma. The diagnosis is usually made on the basis of the presence of flank pain (usually unilateral), fever, rigors, raised C-reactive protein (or erythrocyte sedimentation rate or plasma viscosity), neutrophilia, and evidence of urine infection on culture of a mid- stream urine sample. Although localization studies show a poor cor- relation between the site of infection and the presence or absence of systemic symptoms, the clinical

syndromes of ‘cystitis’ and ‘acute pyelonephritis’ are a robust means of deciding on treatment. Diagnosis Inspection and dipstick testing When typical symptoms are present (more than three of those listed in Box 21.13.3) or if fewer symptoms are present but the urine is cloudy and dipstick urinalysis is positive for nitrite and leucocyte esterase, a diagnosis of UTI likely. In this situation, it is reasonable to make a diagnosis of UTI without further delay and to institute empirical treatment if required. Whether a midstream urine sample should also be sent to the laboratory for confirmation and identifi- cation of the causative organism depends on the clinical situation, as discussed in ‘Laboratory diagnosis and culture of urine’. However, in many situations the diagnosis is not so obvious, and the diagnostic accuracy of inspection and dipstick testing less good. Cloudy urine may be caused by bacteria and pyuria, but may also be caused by amorphous phosphate crystals that form in normal urine as it cools. Low concentrations of bacteria and white cells will not cause sufficient turbidity to be detected on visual inspection. An offensive, fishy smell is highly suggestive of UTI, but relatively infrequent. Visible haematuria can certainly occur as a result of severe cyst- itis, but is frequently absent in isolated UTI and is more often due to glomerular bleeding or urothelial bleeding as a result of tumours or stones. Dipstick detection of haematuria is neither sensitive nor specific for the detection of UTI. Proteinuria can occur in UTI as a result of the release of proteins from white cells, but is neither spe- cific nor sensitive; albumin excretion remains normal unless there is a systemic inflammatory response. Box 21.13.3 Common symptoms of lower UTI • Severe dysuria, often described as ‘scorching’ or ‘like peeing barbed wire’, worse towards the end of or immediately after micturition • Increased urinary frequency • Urgency—the sensation of a strong desire to pass urine • Strangury—the feeling of needing to pass urine despite just having done so • Offensive-smelling urine, often described as ‘strong’ or ‘fishy’ • Visible haematuria • Urge incontinence—leakage of urine associated with the desire to pass urine • Constant lower abdominal aching, not just in the genital area but also in the back, flanks, and lower abdomen • Nonspecific malaise, aching all over, nausea, tiredness, irritability, and cold sweats

 Leucocyte esterase is an enzyme released by white cells and a reliable test for pyuria, which is in most situations a major diag- nostic criterion for UTI, as discussed in the next section. A posi- tive test indicates 10 white cells/ml. Note, however, that transport of urine samples in containers containing boric acid can result in false-negative leucocyte esterase tests, as the boric acid inhibits the enzyme. Nitrite is produced by most uropathogens, which reduce urinary nitrate to nitrite, but not by Gram-positive organisms. A positive test for nitrite is highly suggestive of UTI. False-negative tests can be seen in patients with low dietary nitrate and in those taking high- dose ascorbic acid. The diagnosis of acute uncomplicated UTI is highly likely with a history of two urinary symptoms, and a positive nitrite test. A combination of visual inspection and dipstick testing is a rea- sonable screening test for patients in whom uncomplicated UTI is suspected on clinical grounds: in this situation, crystal-clear urine and negative dipsticks for nitrite and leucocyte esterase make the diagnosis of UTI very unlikely (Table 21.13.1). The worst that is likely to happen if the diagnosis is missed is that the patient will rep- resent with more obvious abnormalities due to progression of the UTI to a more severe stage. However, in situations in which it would be important not to miss the opportunity to start treatment early, for example, in patients with known abnormalities of host defence, pregnancy, or previous acute pyelonephritis, or in suspected atypical infections, formal microscopy and culture of the urine is required. An algorithm for diagnosis of suspected uncomplicated UTI in adult women is shown in Fig. 21.13.2. Laboratory diagnosis and culture of urine The diagnosis of bacterial infection in the urinary tract might appear straightforward, relying on culture of freshly voided urine. However,

urine samples are very easily contaminated during voiding by bac- teria from the perineal skin (or, to a lesser extent, the foreskin in males), resulting in false-positive results. The only certain way to circumvent this problem is to take urine directly from the bladder, either by suprapubic needle aspiration of urine from the bladder, which is invasive and seldom performed in clinical practice, or by urethral catheterization, which carries a 1 to 2% risk of introducing infection into the bladder. In men, contamination of the voided urine sample can largely be avoided by retraction of the foreskin prior to voiding. In women, the reliability of urine culture can be improved by instructing women to part the labia with one hand and Table 21.13.1 Usefulness of inspection and dipstick testing in the diagnosis of UTI Test Utility False positive False negative Cloudy appearance Suggestive Phosphate crystals Common Haematuria Unreliable Renal disease, stones, tumours Common Proteinuria Unreliable Renal disease Common Leucocyte esterase Highly suggestive Some antibiotics Boric acid Nitrite Highly suggestive Few Gram +ve infection Severe or ≥ 3 symptoms of UTI Dysuria Urgency Frequency Polyuria Haematuria AND NO vaginal discharge or irritation 90% culture positive Give empirical antibiotic treatment Consider other diagnosis Urine NOT cloudy 97% NPV Obtain urine specimen Positive nitrite, and leucocytes and blood 92% PPV or Positive nitrite alone Probable UTI Treat with first line agents on local or HPA Guidance Negative nitrite Positive leucocyte Negative nitrite, leucocytes and blood 76% NPV or negative nitrite and leucocyte positive blood or protein Laboratory microscopy for red cells is less sensitive than dipstick UTI Unlikely Consider other diagnosis Reassure and give advice on management of symptoms UTI or other diagnosis equally likely Review time of specimen (morning is most reliable) Treat if severe symptoms or consider delayed antibiotic prescription and send urine for culture Mild or ≤ 2 symptoms of UTI (as above) Perform urine dipstick test with nitrite When reading test WAIT for the time recommended by the manufacturer URINE CLOUDY Suprapubic tenderness URINARY SYMPTOMS IN ADULT WOMEN <65 DO NOT CULTURE ROUTINELY In sexually active young men and women with urinary symptoms consider Chlamydia trachomatis Fig. 21.13.2 Algorithm for diagnosis of suspected acute uncomplicated UTI in adult women. Reproduced with permission from https://www.gov.uk/government/publications/urinary-tract-infection-diagnosis.

section 21 Disorders of the kidney and urinary tract 5080 ensuring collection of a midstream sample, without either the ini- tial portion or the ‘afterdrip’, but is not improved further by perineal washing or antiseptic use. These precautions only reduce the risk of contamination, rather than abolishing it altogether. Microscopy and flow cytometry analysis of urine samples allows quantification of pyuria—the presence of white blood cells in the urine. However, the methodologies used to report pyuria vary enormously. Significant pyuria is usually defined as a urinary white cell count of more than 10 leucocytes/μl of unspun urine. Bacterial UTI is by far the commonest cause of pyuria, and symptomatic patients with pyuria whose urine cultures are reported as showing no significant pathogens should be suspected either of having ‘low-count’ bacteriuria due to early infection, or infection with a slow-growing organism, chlamydial infection, or one of the causes of sterile pyuria (Box 21.13.4). However, vaginal leucorrhoea can also result in ‘false-positive’ pyuria. Once a urine sample is obtained, the conditions under which it is cultured determine whether any organisms present grow. Standard laboratory culture conditions are designed to encourage the growth of recognized urinary pathogens (if present), but may not be optimal for the growth of atypical organisms or of those not usually recog- nized as urinary pathogens. Because small numbers of organisms are frequently cultured from urine as a result of contamination, growth of an organism is conventionally reported as a ‘significant growth’ if it meets several criteria. These are summarized in Box 21.13.5. Although the number of bacteria per

millilitre of urine to diagnose UTI is frequently quoted at greater than 105 cfu/ml, this threshold will miss many cases of UTI. Lower thresholds are therefore applied in some countries (see later in this section). Identification of multiple organisms is often regarded as a sign of contamination. However, genuine mixed growth of two or more bacteria may occur in complicated UTI (Box 21.13.6), as may the growth of an organism not usually associated with the urinary tract. In addition, the spectrum of organisms recognized as capable of causing genuine UTI is widening. S. saprophyticus was only fairly recently recognized as a cause of UTI in sexually active women, and it is possible that other true urinary pathogens are yet to be iden- tified, perhaps accounting for some cases of the so-called urethral syndrome (see 'Urethral syndrome and chlamydial urethritis'). 'Low-count' bacteriuria may reflect genuine bladder infection, particularly in early UTIs, and may occur in patients who have in- creased their fluid intake and are 'diluting' their bacterial counts by generating a high urinary output; also in patients infected with slow- growing organisms such as S. saprophyticus. The criterion of 105 cfu/ml was originally validated in asymp- tomatic women, but subsequent studies showed that nearly 50% of women presenting with frequency and dysuria had genuine bladder infection but with counts between 102 and 105 cfu/ml on culture of a midstream urine sample. If symptomatic women with counts of be- tween 102 and 104 cfu/ml are left untreated, most will have persistent symptoms and counts of more than 105 cfu/ml 2 days later. Current European guidelines advise that the number of colony counts that should be considered to indicate UTI should vary according to the clinical context, for example, with lower counts being accepted as indicative of infection in the presence of symptoms. In the United Kingdom, greater than 104 cfu/ml of a single organism, or greater than 103 cfu/ml of E. coli or S. saprophyticus is regarded as signifi- cant. However, implementation of these criteria by laboratories would require high-quality clinical details to be provided at the time of submission of the urine sample, and most laboratories adhere to the 105 criterion. In men, bacterial counts of 103 cfu/ml or more are very likely to reflect significant infection, as the potential for signifi- cant contamination is lower. The presence of pyuria further increases the likelihood that low counts are significant, although pyuria is not always present in proven bladder infection, particularly if the sample is taken early after the onset. The traditional method of expressing urinary white cell counts as cells per high-power field is very poorly reproducible, as the volume in a high-power field is extremely variable. If accur- ately quantified, the criterion of 10 white cells/mm3 separates pa- tients with genuine bacteriuria from those without. Localization to upper or lower urinary tract Tests to discover whether infection is confined to the bladder or whether it has spread to involve one or both kidneys are very seldom necessary, but may be required if, for example, surgical removal of a kidney because of recurrent infection is contemplated. The 'gold standard' for diagnosis of upper UTI is culture of urine obtained from each ureter by direct catheterization during cystoscopy, but Box 21.13.4 Causes of 'sterile pyuria' • Partially treated bacterial UTI • Bacterial UTI with a 'fastidious' organism • Chlamydial urethritis • 'False-negative' urine cultures due to contamination of midstream urine sample with antiseptic • Contamination by vaginal leucocytes • Chronic interstitial nephritis: — Analgesic nephropathy — Sarcoidosis (urinary white cells may be lymphocytes, not neutrophils) • Urinary tract stones • Acute interstitial nephritis, such as allergic interstitial nephritis (urinary white cells may be eosinophils) • Papillary necrosis: — Diabetes — Sickle cell disease • Renal tract tuberculosis • Fever Box 21.13.5 Criteria for the diagnosis of UTI • There is a pure growth (i.e. of a single organism) • The organism grown is a 'recognized' urinary pathogen • Quantitative urine culture results in greater than 105 cfu/ml • There is significant pyuria on urine microscopy, and few if any squamous cells Box 21.13.6 Conditions in which genuine mixed-growth UTI may occur • Ileal conduits • Neurogenic bladder • Vesicocolic fistula • Urinary

tract stones • Renal abscesses • Long-term indwelling urinary catheters or stents

21.13 Urinary tract infection 5081 such an invasive procedure can only be justified in exceptional cir- cumstances, and even then may be difficult to interpret due to con- tamination of ureteric samples by bladder urine during passage of the catheters. This test is seldom used in modern practice. Renal excretory function usually remains unchanged during acute pyelonephritis unless obstruction is present, but acute kidney injury is occasionally seen, often associated with coincident use of nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, and angiotensin-converting enzyme inhibitors or angiotensin II re- ceptor blockers. Imaging to diagnose pyelonephritis is rarely indi- cated in adults. Abnormal appearances on contrast CT scanning and/or dimercaptosuccinic acid (DMSA) scanning have been re- ported, including generalized renal swelling, focal areas of decreased parenchymal enhancement, and perirenal abscess formation, with the development of cortical scars and calyceal diverticula if imaging is repeated on follow-up. In general, the more severe the infection is clinically (assessed by acute-phase response, duration of fever, etc.), the more marked the radiological abnormality. However, significant loss of renal excretory function following acute pyelonephritis in patients without diabetes, obstruction, or pre-existing reflux neph- ropathy/dysplasia, is remarkably uncommon even on long-term follow-up, and the significance of such scars is therefore uncertain. Differential diagnosis of UTI Occasionally patients may present with symptoms and signs highly suggestive of UTI, with or without pyuria, but with negative urine cultures. These patients may have ‘false-negative’ urine cultures, for example, a low growth of a genuine pathogen; infection with a ‘fas- tidious’ organism, the presence of which is not detected by routine laboratory cultures; or they may have a noninfectious cause. It is dangerous to label symptoms in such patients as psychogenic; pro- longed symptoms combined with numerous unsuccessful trials of antibacterials, or with different explanations from different doctors, may result in psychological stress, which in turn may amplify symp- toms, but there is little evidence that psychological disease is the pri- mary problem, even in a subgroup. Urethral syndrome and chlamydial urethritis The term ‘urethral syndrome’ was used in the past as a synonym for the typical symptoms of cystitis, namely frequency, urgency, and dysuria. More recently it has been applied to the subgroup of women with typical symptoms but in whom a recognized urinary pathogen cannot be cultured from the urine. Some of these patients, particu-larly those with pyuria, have chlamydial urethritis. Chlamydial infection can be confirmed by culture of a urethral swab, or by detection of chlamydia antigens on an endocervical or urethral swab or first-pass urine specimen by nucleic acid ampli- fication techniques. It can be treated with tetracyclines, but as the infection may be sexually transmitted it is also important to treat the patient’s sexual partner(s), who may be asymptomatic. Patients with confirmed chlamydial infection should also be tested for gonorrhoea. Other patients with urethral syndrome have ‘low-count’ infection with a true bacterial urinary pathogen. Vaginal infection or atrophy should be excluded, as these can cause similar symptoms. The pathogenesis and optimal management of the remaining pa- tients with frequency and dysuria, but with no identifiable bacterial infection, remains controversial. There is controversy over the role of ‘fastidious bacteria’ that are difficult to grow in the laboratory, par- ticularly lactobacilli. Empirical antibiotic treatment is equally suc-cessful in eradicating symptoms in women presenting to primary care whether or not urinary pathogens are found on urine culture, suggesting that the syndrome is frequently due to bacterial infection that is not detected by routine laboratory urine culture. However, a few women with persistent symptoms do not respond to antibiotics, and in these women repeated courses of antibiotics are likely to lead to the emergence of antibiotic-resistant organisms, which may later

cause true infection that is difficult to treat. Psychological distress is common in patients with persistent lower urinary tract symptoms, but the prevalence of emotional or psychiatric disorders is no higher in women presenting to general practitioners with dysuria and fre- quency whose urine cultures are negative than in those with proven cystitis. Urologists often offer such women urethral dilatation on the assumption that the symptoms are due to urethral spasm or stric- ture, but there is minimal evidence beyond clinical anecdote that this procedure is of any benefit; one randomized controlled trial showed no difference in outcome between urethral dilatation and cystoscopy alone. Women with recurrent episodes of frequency and dysuria, with or without pyuria, whose urine cultures remain sterile should be carefully evaluated for the presence of vaginitis (either infective or atrophic). It is justified in this situation to obtain urine direct from the bladder during an episode, preferably by suprapubic aspiration or alternatively by urethral catheterization, and ensure that this is cultured in conditions permitting the identification of fastidious or low-growing organisms. In urine obtained direct from the bladder, any growth of organisms is clinically significant. Any infection so detected should be treated, preferably with a prolonged course of an appropriate antibiotic to ensure complete eradication. If no infec- tion can be detected, cystoscopy is required to exclude noninfective causes of cystitis. Painful bladder syndrome/interstitial cystitis Painful bladder syndrome/interstitial cystitis is a chronic bladder syndrome of unknown aetiology. It is characterized by bladder pain (which classically worsens on bladder filling and diminishes with bladder emptying), urgency, frequency, and nocturia, despite—by definition—sterile urine. The syndrome often coexists with other conditions, particularly irritable bowel syndrome. Urine microscopy shows pyuria. Cystoscopy shows variable inflammation, sometimes with ulceration (Hunner’s ulcers, first described in 1914). Bladder biopsies show a chronic inflammatory infiltrate; mast cell infiltra- tion is common, but is also seen in infective cystitis. The condition may progress to cause contracture of the bladder. Many of these features would be explained by an acquired defect in the barrier function of the uroepithelium, but the cause of such a de- fect remains unclear. It remains possible that infection by a fastidious organism is responsible for initiating the disease in some patients. Numerous therapies have been tried, including dietary restriction (citrus fruits, caffeine, alcohol, and carbonate drinks may worsen symp- toms); various oral drugs (pentosan polysulphate sodium, hydroxyzine, amitriptyline, antibiotics, ciclosporin, gabapentin); instillation of intravesical agents including heparin, glycosaminoglycans and bacille Calmette–Guérin (BCG); and most commonly hydrodistension. In severe cases, where all other therapeutic options have failed, bladder augmentation or cystectomy with urinary diversion may be necessary.

section 21 Disorders of the kidney and urinary tract 5082 Drug-induced cystitis This presents similarly, although often more acutely and with visible haematuria. It may be caused by acrolein (a metabolite of cyclophospha- mide), ifosfamide, NSAIDs (particularly tiaprofenic acid), and danazol. Ketamine-induced cystitis Ketamine abuse can result in severe inflammation of the urothelium, associated with decreased bladder compliance and high-pressure vesicoureteric reflux, sometimes resulting in obstructive kidney damage. The syndrome typically presents with severe lower urinary tract symptoms, with urinary frequency, urgency, dysuria, urge in- continence, with or without painful haematuria. On cystoscopy the macroscopic appearances can be mistaken for interstitial cystitis. The histological appearances mimic carcinoma in situ. The natural history remains uncertain, and no treatment has yet been shown to be effective. Radiation-induced cystitis Radiation-induced cystitis is seen in patients who have been treated for bladder or gynaecological malignancy. Clinical investigation—distinction between uncomplicated and complicated UTI The

clinical approach to investigation and treatment of patients with UTI—including whether to send a urine sample for culture, how long to treat for, and whether to send a repeat sample to confirm eradication of infection—depends on making a distinction between ‘uncomplicated’ and ‘complicated’ UTI. Although this is sometimes straightforward—for instance, UTIs in pregnant women and in catheterized patients are, by definition, ‘complicated’—sometimes the decision on whether to investigate for an underlying cause of ‘complicated’ UTI depends solely on the presenting features. Most women with uncomplicated cystitis do not require inves- tigation and may be treated empirically. The yield in such women of investigation with cystoscopy and/or intravenous urography is low. Because minor abnormalities such as duplex collecting sys- tems are common in the general population, these will often be found in women presenting with cystitis, but detection of such ab- normalities does not lead to any change in treatment. Investigation of women should therefore be reserved for those with atypical fea- tures (Box 21.13.7). In men, UTI is associated with an underlying abnormality of host defence in 80% of cases (usually bladder outflow obstruction). Men with proven UTI should therefore be offered investigation, par- ticularly if symptoms do not settle, infection recurs, or haematuria persists. Table 21.13.2 shows the important abnormalities that need to be excluded if investigation is thought to be necessary. Whether adults should be investigated for vesicoureteric reflux is open to doubt, as there is no good evidence that antireflux surgery (e.g. ureteric reimplantation, injection of Teflon around the ureteric orifice) is of benefit in preventing either ascending infection or renal damage. Treatment Uncomplicated asymptomatic bacteriuria The only situations in which treatment of asymptomatic bacteriuria is recommended are during pregnancy and prior to invasive uro- logical surgery; these situations are discussed in later sections. Uncomplicated cystitis Patients with symptomatic lower UTI should be offered symp- tomatic treatment initially with paracetamol, and—if this does not provide symptomatic relief—with an NSAID. The two main aims of antibiotic treatment in UTI are to achieve rapid resolution of symptoms, and to prevent recurrent episodes of infection in the in- dividual patient to minimize the emergence of antibiotic resistance of organisms. Rational treatment of UTI requires the physician to balance the costs and dangers of treatment (including cost of the drug, risk of unwanted side effects, and the induction of resistance) with benefit. Is treatment necessary at all? Many women with recurrent uncom- plicated cystitis report that they can clear their own infections by increased fluid intake and frequent voiding. Many buy alkalinizing agents (e.g. potassium citrate) to ameliorate the symptoms, which work by reducing bladder irritability. Placebo-controlled studies and studies comparing NSAIDs with antibiotics have confirmed that uncomplicated infections in women will usually clear spontan- eously. Antibiotics reduce the duration of symptoms by 1 to 2 days. Antibiotics could therefore be avoided in patients with mild symp- toms, and reserved for those with more severe symptoms and those who express a strong preference for antibiotic treatment. An alter- native approach is to delay the introduction of antibiotics for 48 h Box 21.13.7 Indications for further investigation in females with UTI • Genuine mixed growth • Failure of standard antibiotic treatment to eradicate infection • Relapsing infection (repeated detection of the same organism, as iden- tified by antibiotic sensitivity pattern, or more detailed typing) • Confirmed infection with organisms not usually recognized as uropathogens • Infection with Proteus spp. • Marked acute-phase response (or symptoms of ‘acute pyelonephritis’), suggesting tissue invasion • Persistent haematuria after treatment of infection Table 21.13.2 Clinical investigation of UTI Abnormality to be excluded Investigation Diabetes Blood test Urinary tract stones Ultrasonography as first-line imaging and plain radiography (KUB), intravenous urography, CT urography if indicated Anatomical abnormalities of the upper tract (e.g. papillary necrosis, reflux nephropathy) Urinary tract obstruction Bladder diverticula Cystoscopy

Impaired bladder emptying Urinary flow studies KUB, kidneys–ureters–bladder.

21.13 Urinary tract infection 5083 to allow the infection to clear spontaneously, a strategy that—when offered—is chosen by a high proportion of patients. Choice of antibiotic It is usually impracticable to await the results of culture and sen- sitivity testing, and in most cases such tests are not justified. The choice of antibiotic is therefore usually empirical, based on the likeli- hood that the drug will clear the infection (efficacy), cost, side effect profile, and the risk of selection of resistant organisms, both in the patient being treated and in the community. The efficacy of antibiotics is not fully predictable from in vitro sen- sitivity testing, which is probably part of the reason why trimetho- prim (with or without sulphamethoxazole) remains the first-line choice in many areas, despite an upward trend in resistance rates. This is at least in part because many antibiotics are concentrated in the urine to levels far greater than those found in tissues, and at these concentrations may remain active against organisms that are reported to be resistant to the concentrations found in tissues, which are usually used to define resistance in vitro. Trimethoprim is also concentrated in vaginal secretions by 'ion trapping'. However, increasing resistance in vitro to trimethoprim is sure to lead sooner or later to increased clinical failure rates, as has already been ob- served for β-lactam antibiotics. Some of the clinical properties of the most commonly used antibiotics are reviewed in Table 21.13.3, with the target and mechanisms of actions of different antibiotic agents shown in Fig. 21.13.3. The 2018 recommendations of the National Institute for Health and Care Excellence (NICE) for treatment of UTI are summarized in Table 21.13.4. Duration of treatment Although a single high dose of an antibiotic will cure many women with uncomplicated lower UTI, cure rates are higher with 3-day courses and higher still with 7-day courses. However, the risk of ad- verse effects is also related to the duration of treatment. Alternatives to antibiotic therapy Cranberry juice and tablets, methenamine hippurate, and treatment of atrophic vaginitis with topical oestrogens have all been used in the prevention of UTI (see later sections), but there is no proven role for any of these interventions in the treatment of an established UTI. Uncomplicated 'acute pyelonephritis' Choice of antibiotic The antibiotic chosen in this situation needs good tissue penetration as well as high urinary excretion, and must be fully active against the infecting organism at typical serum concentrations. It is there- fore much more important to identify the infecting organism and its antibiotic sensitivity pattern by sending urine (or blood from pa- tients in hospital) for culture. However, empirical treatment must be started while awaiting culture and sensitivity results, as acute pyelonephritis can evolve rapidly into a life-threatening illness. Oral therapy with a quinolone antibiotic (ciprofloxacin, ofloxacin, norfloxacin) is probably the best choice, although treatment with co- amoxiclav (or trimethoprim or trimethoprim–sulphamethoxazole if local resistance rates are low) are alternatives. Treatment with a β- lactam antibiotic alone, even if the infecting organism is fully sensitive in vitro, is associated with a high rate of recurrence compared with treat- ment by other agents. Patients with septicaemia should receive a quin- olone (for which oral administration is as effective as intravenous) or Cell wall synthesis Pencillins Daptomycin Cephalosporins Carbapenems Glycopeptides MurA inhibitors Siderophore – β- lactam antibiotics Cell wall PABA Efflux pump inhibitors DNA Gyrase/Topoisomerase Quinolone Folic-acid- metabolism Dihydrofolate- reductase-inhibitors Trimethoprim Sulfonamides 50S Inhibitors Linezolid Nitrofurantoin 30S Inhibitors Tetracyclines Tigecycline Aminoglycosides Nitrofurantoin Cell membrane DNA DHFA THFA Ribosome Fig. 21.13.3 Targets and mechanisms of actions of different antibiotic agents used in the treatment of UTI. DHFA, dihydrofolic acid; PABA, p- aminobenzoic acid; THFA, tetrahydrofolic acid. Reprinted from European Urology, 49(2), 235–44, Wagenlehner FME and Naber KG, Treatment of

Bacterial Urinary Tract Infections: Presence and Future. Copyright © 2005, with permission from Elsevier. Table 21.13.3 Clinical properties of antibiotics commonly used for UTIs Antibiotic Advantages Disadvantages Trimethoprim Cheap Well tolerated High concentrations in vaginal and periurethral fluid Increasing rates of in vitro resistance Trimethoprim– sulphamethoxazole As for trimethoprim Possible reduced risk of emergence of resistant strains Increasing rates of resistance Adverse reactions (e.g. rash) to sulphonamide component Not licensed for the treatment of UTI in some countries β-Lactams (e.g. amoxicillin, cephalosporins) Cheap Well tolerated High rates of resistance Less effective than trimethoprim in 3-day or single-day regimens Allergic reactions High risk of Clostridium difficile colitis β-Lactams with β- lactamase inhibitor (e.g. co-amoxiclav) As for β-lactams Low rates of resistance Cost Risk of selection of resistant strains Allergic reactions High risk of Clostridium difficile colitis Nitrofurantoin Cheap Does not induce resistance in bowel organisms Nausea and vomiting (less with macrocrystalline preparations) Hepatic, neurological, haematological, and pulmonary toxicity (mostly seen with prolonged treatment) Less effective in patients with low glomerular filtration rates Quinolones, e.g. ciprofloxacin Well tolerated Broad antibacterial spectrum including many uropathogens Cost High risk of Clostridium difficile colitis Achilles tendon damage

section 21 Disorders of the kidney and urinary tract 5084 a combination of an aminoglycoside with ampicillin plus β-lactamase inhibitor, or an extended-spectrum cephalosporin with or without an aminoglycoside. Once-daily administration of aminoglycosides is as effective as thrice-daily and reduces the risk of toxicity. Duration of therapy It is widely recommended that acute pyelonephritis is treated with a significantly longer course of antibiotics than acute cystitis (Table 21.13.4). It is therefore reasonable to suggest that in a patient with systemic symptoms (including flank pain) and fever; or leuco- cytosis, or a raised C-reactive protein; antibiotic treatment should be continued until these abnormalities have disappeared. A 7-day course of a quinolone antibiotic should be sufficient for most pa- tients, but longer courses of antibiotic treatment may be required for other antibiotics or if symptoms persist. . Prevention of recurrent uncomplicated UTI Advice about personal hygiene and other matters It is common practice to advise women with UTIs to void after inter- course, practise double micturition, wipe themselves from front to back after micturition, and increase their fluid intake. A systematic review concluded that the evidence for such advice was not based on good evidence, and stated ‘routine advice about adopting or discontinuing any particular lifestyle factors should not be offered to patients with bacterial UTI’. However, absence of evidence of benefit is not the same as evidence of absence of benefit, and for individuals with recurrent and/or complicated UTI, individualized advice along these lines is reasonable. Long-term prophylactic antibiotics Some women with recurrent cystitis choose to have antibiotic treat- ment for each infection as it arises, particularly if they are allowed to self-administer treatment as soon as symptoms start. Others may opt for prophylactic treatment. Long-term, low-dose antibiotic treat- ment is effective in reducing the rate of infection in such women, al- though not to zero, and with a significant risk of adverse effects (e.g. gastrointestinal symptoms, rash, vaginal irritation). Prophylactic treatment should be considered in women with at least two symp- tomatic infections per year and probably works by preventing colon- ization of periurethral tissues by uropathogens. Trimethoprim (100 mg at night) is widely used for prophylaxis be- cause it achieves very high concentrations in vaginal fluid and may therefore remain active against organisms that are resistant to the concentrations used in in vitro sensitivity testing. Nitrofurantoin (100 mg at night) has also been widely used, and may be more ef- fective, but can cause rare but serious adverse effects (pulmonary and hepatic toxicity) with long-term therapy, making regular moni- toring of

liver enzymes and lung function tests necessary. Because both are well absorbed they do not reach high concentrations in the colon, hence emergence of resistant strains in colonic flora is uncommon, whereas this problem does arise with long-term use of β- lactam antibiotics. Long-term use of quinolones is associated with a significant risk of selection of resistant strains, and also carries a risk of Achilles tendon rupture. A number of dosage regimens have been used, including nightly treatment, thrice-weekly treatment, and postcoital treatment, with no convincing evidence of the superiority of one regimen over another. There is no evidence to support the use of 'rotating' antibiotic prophylaxis. Table 21.13.4 NICE recommendations for the treatment of symptomatic lower UTI in the community Uncomplicated UTI in women, i.e. no fever or flank pain Use urine dipstick to exclude UTI –ve nitrite and leucocyte 95% negative predictive value There is less relapse with trimethoprim than cephalosporins or pivmecillinam. Community multiresistant E. coli with extended-spectrum
β-lactamase enzymes (ESBLs) are increasing so perform culture in all treatment failures. ESBLs are multiresistant but remain sensitive to nitrofurantoin Trimethoprim OR nitrofurantoin 200 mg BD 100 mg (modified release) BD 3 days Second choice—depends on susceptibility of organism isolated, e.g. nitrofurantoin, pivmecillinam, fosfomycin UTI in pregnancy Send MSU for culture. Avoid use of nitrofurantoin at term because of risk of neonatal haemolysis Nitrofurantoin Second choice: Cefalexin OR amoxicillin 50–100 mg QDS 500 mg BD 500 mg TDS 7 days 7 days 7 days UTI in men Send MSU for culture Timethoprim OR nitrofurantoin 200 mg BD 100 mg (modified release) BD 7 days 7 days Second choice—depends on susceptibility of organism isolated, e.g. cefalexin, co-amoxiclav, trimethoprim, ciprofloxacin Children Send MSU for culture and susceptibility Waiting 24 h for results is not detrimental to outcome Trimethoprim OR nitrofurantoin Second choice: Nitrofurantoin, amoxicillin (if susceptible), cefalexin See BNF for dosage 3 days Acute
pyelonephritis Send MSU for culture. A recent randomized controlled trial showed 7 days ciprofloxacin was as good as 14 days co-trimoxazole If no response within 24 h—admit to hospital Cephalexin recommended in pregnancy Ciprofloxacin OR co-amoxiclav
(if susceptible) OR trimethoprim
(if susceptible) 500 mg BD 500/125 mg TDS 200 mg BD 7 days 7–10 days 14 days Recurrent UTI in women Post coital prophylaxis is as effective as prophylaxis taken nightly. Nitrofurantoin OR trimethoprim 50–100 mg at night or 100 mg post coital 100 mg at night or 200 mg post coital BD, twice daily; BNF, British National Formulary; MSU, midstream urine; QDS, four times daily; TDS, three times daily.

 Box 21.13.8 Possible causes of UTI in men • Bacterial prostatitis and prostatic calcification • Lack of circumcision • Impaired bladder emptying (particularly if this has resulted in bladder catheterization or instrumentation) • Anal intercourse • Urinary tract stones • Reflux nephropathy Other treatments Cranberry juice or tablets Cranberry juice contains proanthocyanidin, which inhibits adher- ence of P-fimbriated E. coli. Cranberry products are not regulated and the concentration of the active ingredient varies considerably. To date, the clinical evidence that regular ingestion of cranberry juice or tablets can prevent UTIs remains unconvincing. Methenamine hippurate Methenamine is hydrolysed in acid urine to produce formaldehyde, a powerful antiseptic. Use of this drug is not associated with the emergence of antibiotic resistance. Its effectiveness may be enhanced by urine acidification, achieved for instance by coprescribing high- dose ascorbic acid. A 2012 Cochrane review found that the evidence base was limited, but that methenamine reduced the risk of UTIs among women with

anatomically normal urinary tracts (relative risk of symptomatic UTI 0.24, 95% confidence interval 0.07–0.89), but not among patients with known urinary tract abnormalities. Treatment of atrophic vaginitis There is significant heterogeneity in the results of trials examining the effects of topical oestrogens on prevention of recurrent UTIs. This may be due to differences in inclusion criteria. Oestrogens are not recommended for the routine prevention of recurrent UTIs in postmenopausal women, but they may be of benefit in individuals with marked atrophic vaginitis. Vaginal oestrogens can cause side effects including breast tenderness and vaginal bleeding, discharge, and irritation. Probiotics Attempts to prevent recurrent urinary infection by re-establishing colonization by lactobacilli have so far not yielded convincing evi- dence of benefit. Vaccines Vaccination is an attractive option for the prevention of UTI. There is evidence from preclinical studies that vaccination can reduce in- fection rates, but there is no convincing evidence that it does so in humans. UTI in particular circumstances UTI in men UTI in men is uncommon, as the length of the urethra and the fact that the penile mucosa is seldom colonized with faecal organisms including uropathogens confer major protection against ascending infection. The occurrence of UTI in a man therefore suggests an ab- normality of host defence, which may predispose to more severe in- fection and should be investigated unless the cause is immediately obvious (e.g. the presence of a urinary catheter). Risk factors that may be identified by investigation are listed in Box 21.13.8. Prostatitis Prostatitis is a common cause of visits in primary care and of uro- logical referrals. It can cause considerable morbidity, and patients may remain symptomatic for years. The National Institutes of Health consensus classification of prostatitis syndromes is summarized in Box 21.13.9. Acute bacterial prostatitis Acute bacterial prostatitis causes fever, rigors, backache, and dys- uria, and may result in acute urinary retention. Symptoms and signs of epididymitis may also be present. Rectal examination reveals an enlarged, tender prostate. Bacteriuria and pyuria are frequently pre- sent. Untreated, acute prostatitis may culminate in prostatic abscess formation, so ultrasonography of the prostate should be requested in patients who do not respond promptly to antibiotic treatment. The causative organism (commonly E. coli) can be identified on urine culture. An antibiotic that has good tissue penetration (e.g. trimethoprim, a tetracycline, or a quinolone) should be used and continued for 4 weeks, as it is thought that this reduces the risk of chronic prostatitis. Chronic bacterial prostatitis This is an uncommon syndrome caused by the persistence of a uropathogen (usually Gram-negative organisms or enterococcus) within the prostate, with repeated episodes of acute infection caused by the same organism on each occasion, and few if any symptoms between episodes. Obtaining bacteriological proof that the infecting organism is ‘hiding’ in the prostate gland between acute episodes is difficult. The ‘textbook’ method described by Stamey and Mears involves culture of four specimens obtained during voiding of the bladder: the first 10 ml voided and a midstream sample are col- lected; the patient then interrupts the flow of urine, bends forward, and digital prostatic massage is performed, resulting (sometimes) in the collection of a few drops of ‘expressed prostatic secretions’; fi- nally, voiding is completed and a fourth sample collected. Prostatitis is diagnosed when bacterial counts are highest in the expressed prostatic secretions and the final voided urine sample; urethritis, by contrast, results in high counts in the first sample. Because of its complexity and the unpleasantness of performing digital prostatic Box 21.13.9 National Institutes of Health classification of prostatitis syndromes • Acute bacterial prostatitis • Chronic bacterial prostatitis • Chronic prostatitis/chronic pelvic pain syndrome: A Inflammatory B Noninflammatory • Asymptomatic inflammatory prostatitis Adapted from National Institutes of Health classification of prostatitis syn- dromes, with permission.

section 21 Disorders of the kidney and urinary tract 5086 massage per rectum during interrupted micturition, this test is very rarely performed in practice, and many patients are simply treated with a prolonged course of a quinolone antibiotic. α-Blockers have been shown to reduce recurrence rate, possibly by reducing reflux of urine into prostatic ducts during micturition. Acute and chronic bacterial prostatitis are the best understood but least common of the prostatitis syndromes. More than 90% of symptomatic patients have chronic prostatitis/chronic pelvic pain syndrome. Chronic prostatitis/chronic pelvic pain syndrome Chronic urological pain is the primary component of this disorder. Patients may also complain of dysuria, strangury, urinary frequency, and pain during sexual intercourse, but have no evidence of bacterial infection on cultures of prostatic secretions, semen, or post-massage urine specimens. Certain conditions must be excluded, including active urethritis, urological cancer, significant urethral stricture, or neurological disease affecting the bladder. Patients with this symptom complex may be further subclassified as having inflammatory or noninflammatory pelvic pain syn- drome according to the presence or absence of leucocytes in semen. Occasionally, patients are found to have evidence of prostatic in- flammation on biopsy, or to have leucocytes in prostatic fluid in the absence of symptoms, in which case they are regarded as having asymptomatic inflammatory prostatitis. Treatment There is no gold standard for diagnosis, nor a clear understanding of the pathophysiology, no correlation between symptoms and pros- tatic histology, and no satisfactory treatment for this ill-understood group of conditions. As in the urethral syndrome in women, some cases may be caused by persistent infection by fastidious bacteria, such as chlamydia or mycoplasma; a prolonged trial of a tetracyc- line is therefore often used. Other treatments include regular pros- tatic massage, NSAIDs, α-blockers, and 5-α reductase inhibitors. α-Blockers have been shown to be of some benefit in all types of symptomatic chronic prostatitis in one randomized study.

Urethral catheterization UTI occurs after 2% of in/out urethral catheterizations, after 10 to 30% of 5-day indwelling catheterization, and is nearly inevitable in patients with long-term indwelling catheters. It is an important cause of hospital-acquired infection, increasing the risk of Gram-negative septicaemia fivefold and carrying a threefold increase in mortality after adjustment for age, severity and type of underlying illness, duration of catheterization, and renal function. Organisms enter the bladder either by migration between the catheter and the urethral mucosa or by ascent up the column of urine in the lumen after entry into the drainage system following contamination at dis- connection or drainage points. Although most infections are prob- ably caused by ascent of the patient’s own faecal flora, investigation of clusters of infections by highly antibiotic-resistant organisms showed that inadequate hand-washing by hospital staff may also cause some infections. A sample obtained directly from the catheter (not from the drainage bag) represents bladder urine, when any bacterial growth should be considered as evidence of UTI; low-count infection (e.g. <102 cfu/ml) usually progresses within days to higher counts. Mixed growths are common in patients with long-term catheterization and may be associated with mixed-growth bacteraemia. Risk factors for the acquisition of infection include increasing duration of catheterization, increasing age, female sex, renal im- pairment, diabetes mellitus, and the nature of the underlying illness. Use of prophylactic antibiotics is associated with a delay in the onset of infection and may be justified in high-risk patients re- quiring catheterization for at least 24 h and up to 14 days, whereas in those with long-term catheters, use of prophylactic antibiotic simply increases the risk of emergence of antibiotic-resistant patho- gens without any benefit. Use of silver alloy-coated catheters, or use of antibiotic-impregnated catheters, also reduces the risk of infec- tion in the short term, but not in long-term catheterization, and may be justified in high-risk patients; no direct comparisons of these two interventions have been performed; both are more ex-

pensive than standard catheters, and the balance of cost and benefit remains uncertain. Progress is being made in the development of new catheter materials that may provide further resistance against colonization by microorganisms. Urethral catheters should not be inserted unless absolutely neces- sary (is knowledge of hourly urinary output really going to change your management?). Early removal of urethral catheters reduces the risk of symptomatic UTI. Suprapubic catheters are associated with lower risks of UTI and a lower rate of recatheterization in postsurgical patients, but their use may be associated with a higher risk of com- plications. If a urethral catheter is used, catheter care should follow appropriate guidelines (e.g. as provided by the National Institute for Health and Care Excellence in the United Kingdom). There is some evidence that antibiotic prophylaxis at the time of catheter removal can reduce the risk of subsequent symptomatic UTI. Clean intermittent self-catheterization should be considered as an alternative to long-term urethral catheterization. Whether prophy- lactic antibiotics further reduce the risk of UTI among patients undertaking intermittent self-catheterization remains uncertain. Condom drainage should be used as an alternative to urethral catheterization for incontinence in men unless there is obstructive nephropathy; this form of bladder drainage reduces the risk of UTI fivefold and is better tolerated. Treatment of asymptomatic bacteriuria in patients with anatom- ically abnormal urinary tracts or with indwelling urinary catheters is unjustified and is likely only to lead to the emergence of antibiotic- resistant urinary infection. Abnormal bladder emptying Incomplete bladder emptying, removing the ‘washout’ part of host defence, greatly increases the risk of UTI, as in patients with prostatic bladder outflow obstruction and those with neurogenic bladder due to spinal cord injury. Long-term catheterization only increases these risks. Where possible, the cause of incomplete bladder emptying should be treated. However, patients shown on urodynamic study to have underactive detrusor activity will not benefit from pros- tatectomy or α-blockade and may require long-term intermittent self-catheterization. Bladder dysfunction in patients with neurogenic bladder (e.g. due to spina bifida or spinal cord injury) depends on the level of injury. Patients with lesions above T11 have hyperreflexic bladder activity, often with sphincter dyssynergia (failure of the sphincter to relax during detrusor contraction), resulting in a high-pressure system,

 often with high-pressure reflux, combined with impaired emptying. In combination with UTI, this frequently results in progressive renal damage. Those with lesions below L1 have decreased detrusor ac- tivity with large amounts of residual urine, which also increases the risk of UTI. Diabetic neuropathy may also cause decreased de- trusor activity. The aim of treatment in both situations is to achieve a low-pressure bladder with low residual volumes. This may involve teaching patients to utilize reflexes to induce bladder contraction and sphincter relaxation, condom drainage for incontinence, anticholin- ergics to reduce detrusor overactivity, sphincterotomy, augmenta- tion cystoplasty, and intermittent self-catheterization. Long-term urethral catheterization should be avoided wherever possible. There is no evidence that regular use of antiseptics to wash the perineum and urethral meatus are of benefit. Bladder washouts with saline or boiled (and then cooled to body temperature) water may be of benefit in eliminating mucus in patients with augmentation cystoplasties. Antiseptic bladder washouts are of minimal value in prevention, probably because uropathogens become embedded in a biofilm adherent to the bladder wall. Treatment of UTI in patients with abnormal bladder emptying should be reserved for those with evidence of invasive infection. The diagnosis is obvious in those with cloudy urine combined with fever, rigors, and flank pain, but it is important to remember that symptoms and signs—particularly flank pain, dysuria, urgency, and frequency—may be absent in those with

neurological dysfunction. Urological surgery Patients with asymptomatic bacteriuria who undergo invasive uro- logical procedures that are associated with mucosal bleeding are at high risk of postprocedure bacteraemia and clinical sepsis syn- dromes, and there is evidence that preoperative antibiotic treatment of asymptomatic bacteriuria (ideally, the night before the procedure, continued until completion or removal of an indwelling catheter, whichever is the later) reduces these risks. Urinary diversion Ileal or colonic conduits have been used for many years in patients requiring cystectomy for malignancy, and occasionally (although increasingly less frequently) for nonmalignant conditions such as neurogenic bladder. Such conduits are frequently complicated by urine infection, as the bowel mucosa and the mucus it produces readily permits adherence of uropathogens. Upper urinary tract dilatation is common, irrespective of whether the ureteric anasto- moses are designed to be nonrefluxing or not, and there is a high incidence of recurrent ‘acute pyelonephritis’ with flank pain, fever, and rigors. Diagnosis of UTI in patients with a conduit requires insertion of a catheter to the far end of the conduit and collec- tion of urine via the catheter, rather than culture of urine collected from the conduit bag. Preventive measures include ensuring that the ileal segment is as short as possible at the time of surgery and ensuring a high fluid intake. The belief that cranberry juice reduces the incidence of UTI by reducing bacterial adherence is as yet un- proven, although it seems probable that treatments designed to interfere with bacterial adherence or with mucin production are more likely than antibiotic treatment to help prevent symptomatic infection in these patients. Urinary tract stones Urinary tract stones are an important cause of persistent or relapsing UTI, as they provide a ‘hiding place’ in which organisms are protected from antibiotics. Management of such patients is complicated, as it may be impossible to eradicate infection without aggressive stone management (which may involve extracorporeal shock-wave litho- tripsy, percutaneous and ureteroscopic stone removal). Attempts at stone removal may be complicated by septicaemia unless combined with antibiotic treatment, yet prolonged antibiotic therapy may en- courage the emergence of resistance in the infecting organism. Infection stones are caused by chronic infection with urease- producing organisms, usually Proteus mirabilis, and account for around 5% of urinary tract stones. These stones are made of struvite ($MgNH_4PO_4.6H_2O$), which forms as a result of the action of the al- kaline pH caused by the production of ammonium and hydroxyl ions from the breakdown of urea by urease. Pure struvite stones may result from de novo UTI by a urease-producing organism, and are commoner in women and (probably) in patients with pre-existing anatomical abnormalities of the upper urinary tract such as reflux nephropathy, pelviureteric junction obstruction, or urinary diver- sion. They may also form as a secondary complication of metabolic stones. Struvite stones often expand to fill the entire renal pelvis, forming ‘staghorn’ calculi, but such calculi should not be assumed to be due to infection (rather than a metabolic cause) without demon- stration of chronic infection by a urease-producing organism and/or biochemical analysis showing that the stone is made of struvite. The usual presentation is with symptomatic ‘acute pyelonephritis’ and al- kaline urine; renal colic is unusual due to the large size of the stones. Treatment is with a combination of antibiotics and stone removal, which is imperative to prevent stone recurrence. Urease inhibitors (acetohydroxamic acid, propionhydroxamic acid) may reduce stone recurrence but are too toxic for clinical use. See Chapter 21.14 for further discussion. Autosomal dominant polycystic kidney disease Cystitis is common in women with polycystic kidney disease, and in 20% it is the presenting clinical finding, but there is no evidence that host defence in the lower urinary tract is abnormal. However, the risk of upper UTI is increased, and its diagnosis and treat- ment complicated. Acute parenchymal infection presents as acute pyelonephritis with flank pain, fever, and infected bladder urine, and usually responds to conventional therapy. Infection of cysts is more

difficult to diagnose: the urine may be sterile and there may be no pyuria if the infected cyst does not communicate with the urinary space. Presentation is with fever and a discrete area of tenderness in the affected kidney. Blood cultures are the most re- liable way of making a bacteriological diagnosis. Imaging studies, looking for cysts with increased fluid density, septations, and thick walls, are seldom conclusive, as similar appearances may occur normally or after previous cyst haemorrhage. The spectrum of causative organisms suggests that ascending infection rather than haematogenous spread is the usual route of infection. Hydrophilic antibiotics, including aminoglycosides and β-lactam antibiotics, penetrate poorly into those cysts that maintain large ionic gradients, whereas quinolones, trimethoprim–sulphamethoxazole, doxycyc- line, and clindamycin achieve better penetration. Prolonged courses

 of antibiotics are usually needed to eradicate infection, with surgical resection a last resort. Renal transplantation UTI is the commonest bacterial infection after renal transplant- ation. Risk factors include urethral catheterization in the early postoperative period, the use of ureteric stents, pre-existing abnor- malities of bladder emptying (such as diabetic autonomic neur- opathy, previous bladder outflow obstruction, and small contracted bladders in anuric patients on dialysis), anatomical abnormalities in the upper urinary tract (such as reflux nephropathy), contam- ination of the transplanted organ during retrieval and storage, abnormal drainage of urine from the transplanted kidney, vesico- ureteric reflux into the transplant, areas of renal infarction, and immunosuppression. The commonest causative bacteria are those found in the general population with UTI, but many organisms not usually considered as urinary tract pathogens may also cause significant infection in these patients. Many infections are asymp- tomatic. Prophylactic antibiotics may reduce the early postoperative risk and many centres use co-trimoxazole as it also reduces the risk of pneumocystis pneumonia. Antibiotic treatment must be chosen with care because of the risk of interactions with immunosuppres- sive treatment and of nephrotoxicity. The impact of isolated lower UTIs in transplant recipients is dif- ficult to quantify because there may be coexisting upper tract in- fection. Many transplant recipients (7–40%) with symptoms of cystitis go on to develop graft pyelonephritis, which is an inde- pendent risk marker for subsequent reduced graft function, graft loss, and increased mortality. In transplant recipients, asymptom- atic bacteriuria is common and associated with an increased risk of developing graft pyelonephritis. Although treatment of asymptom- atic bacteriuria in transplant recipients appears to reduce the risk of graft pyelonephritis, there is no evidence that treatment improves transplant outcome. Although screening, treatment of asymptom- atic patients, and long-term antibiotics are strategies used post transplantation, more research is required to determine whether this has any positive effect on long-term outcomes. Infection with Corynebacterium urealyticum can cause ‘en- crusted pyelitis’ in transplant kidneys, in which the pelvis of the transplant kidney becomes encrusted with calcified material, which can cause obstruction and thus transplant dysfunction. The CT appearances are characteristic (Fig. 21.13.4). The calcification comprises struvite (magnesium ammonium phosphate), as in in- fection stones. Management is difficult, and comprises prolonged antibiotic therapy and surgical excision of the calcified material, if possible. Infection with BK virus (a polyoma virus) may cause cystitis, ur- eteric stenosis, and interstitial nephritis (easily mistaken for acute rejection) in renal transplant recipients. The diagnosis may be sug- gested by recognition of infected transitional uroepithelial cells on urine cytology (‘decoy’ cells), quantitative polymerase chain reac- tion of blood and urine for BK virus, and confirmed by histological recognition of inclusion bodies and immunostaining for the BK virus (or SV40) large T antigen on renal biopsy.

Treatment is by re- duction of immunosuppression, but this is often complicated by fur- ther rejection. Pregnancy Asymptomatic bacteriuria early in pregnancy is associated with the development of acute pyelonephritis in up to 30% of patients (20– 30 times the risk in women without bacteriuria) if left untreated. It is commoner in women of lower socioeconomic status and is as- sociated with an increased incidence of preterm delivery and low birth weight, particularly if the pregnancy is complicated by acute pyelonephritis towards term. The increased risk of pyelonephritis is attributed to ureteric dilatation caused primarily by progesterone- induced smooth muscle relaxation. Antibiotic treatment of asymptomatic infection reduces the risk of acute pyelonephritis and of preterm delivery and low birth weight. Similar benefit is seen from a short course of treatment and from continued antibiotic prophylaxis. The choice of initial anti- biotic should be based on local resistance patterns. Nitrofurantoin has the best safety record in pregnancy: alternatives are shown in Table 21.13.4. Current guidelines support the use of a 7-day course of antibiotics in symptomatic UTI in pregnancy. Follow-up urine cultures at each antenatal visit should be performed to ensure that bacteriological cure has been achieved. (See Chapter 14.5 for further discussion.) Reflux nephropathy Vesicoureteric reflux (retrograde flow of urine up into the ureters and, in severe cases, as far as the renal pelvis and kidney) is often found in children with recurrent UTI. At the time of first diagnosis of UTI or subsequently, a few such children are found to have a characteristic pattern of renal parenchymal scarring at the upper and lower poles, with underlying clubbing and distortion of calyces. This pattern of scarring has become known by a variety of terms, including ‘reflux nephropathy’ and ‘chronic pyelonephritis’. Patients with reflux neph- ropathy have an increased risk of recurrent UTI, may develop stones, and some develop hypertension, proteinuria, and progressive renal impairment with an inexorable progression to endstage renal failure. Under the age of 1 year, when only relatively severe cases come to clinical attention, slightly more boys than girls are affected; in older Fig. 21.13.4 CT scan of transplant kidney with calcification of the renal pelvis (arrows) due to encrusting pyelitis.

 children, the disease is diagnosed up to five times more frequently in girls, possibly because the disease is often discovered during investi- gation of UTI, which is commoner in females. Reflux nephropathy is commonly familial, best modelled by an autosomal dominant pat- tern of inheritance with variable penetrance. The diagnosis of reflux nephropathy is conventionally made in adults by intravenous urography or CT urography, which permits the detection both of focal parenchymal scarring and the underlying calyceal abnormality (Fig. 21.13.5). Ultrasound scanning can show focal scarring but does not allow visualization of the calyces. DMSA isotope scanning is the most sensitive test for the detection of paren- chymal scars, and is widely used in children, as there are few alterna- tive causes of focal scarring in this age group. Lateral displacement of the ureteric orifices can be demonstrated by Doppler ultrasonog- raphy in most patients with reflux nephropathy. Demonstration of vesicoureteric reflux by direct or isotopic micturating cystography is commonly used to confirm the diagnosis in children, but is rarely justified in adults, as the absence of reflux could be due to spontan- eous resolution of reflux with age (it often resolves in childhood), and its presence seldom justifies a change in clinical management. The histological appearances of ‘chronic pyelonephritis’ are well de- scribed and may occasionally be seen in patients with no scarring on urography or even DMSA scanning, probably because the scars are too small in these patients to be detected radiologically. The conventional view is that reflux nephropathy is ‘postinfectious focal renal scarring’ and caused by the ascent of infected urine into the renal pelvis and then into the collecting ducts and renal paren- chyma via compound papillas (papillas in which more than one col- lecting duct opens into the pelvis). These

are found at the upper and lower poles, but not in the middle calyces—explaining the polar distribution of scars. Sequential radiological imaging studies in children with UTIs appear to support this theory, with the emergence of new scars up until the age of around 5 years, after which it is thought that maturation of the papillas prevents entry of infected urine into the renal parenchyma. Experimental infection in pigs causes a pattern of scarring very similar to that seen in human reflux nephropathy. An alternative hypothesis is that at least some children with the radiological diagnosis of reflux nephropathy have congenital renal dysplasia, caused by abnormal nephrogenesis in utero, and as- sociated abnormal embryogenesis of the ureterovesical junction leading to vesicoureteric reflux. Vesicoureteric reflux is often found in various genetic syndromes that include renal dysplasia, and in nonsyndromic renal dysplasia or aplasia, vesicoureteric reflux in the contralateral ureter is commonly seen. This theory would explain the presence of classic reflux nephropathy in neonates and in chil- dren with no documented history of UTI. Even the emergence of new scars during the first 5 years of life could be due to differen- tial growth around areas of renal dysplasia. The rarity with which acute pyelonephritis in adults results in renal impairment, even in the presence of radiological evidence of scar formation, is perhaps further evidence that progressive loss of renal function is more likely to be due to ‘remnant nephropathy’ in dysplastic kidneys rather than the result of postinfectious scarring alone. These two hypotheses have different implications for the preven- tion of reflux nephropathy. Proponents of the ‘postinfectious focal renal scarring’ theory believe that diagnosis in infancy and treat- ment to prevent the ascent of infected urine into the renal pelvis until at least the age of 5 years should prevent the emergence of renal scarring and the later sequelae of hypertension, proteinuria, and progressive renal failure; by contrast, such treatment will not prevent these sequelae if reflux nephropathy is a disease of em- bryogenesis. Of course, the two theories are not mutually exclusive: in an individual patient, reflux nephropathy may be due to the interaction of dysplasia and ascending infection during infancy. Antireflux surgery (ureteric reimplantation) and long-term prophy- lactic antibiotic treatment have been compared in several large ran- domized trials. Surgery is more effective at preventing episodes of acute pyelonephritis than medical treatment, but no other major differences in outcome were observed, and potential complica- tions of antireflux surgery include ureteric obstruction, itself a po- tent cause of renal parenchymal damage. In modern practice, open surgical ureteric reimplantation is now seldom performed, having been replaced by endoscopic techniques involving subureteric or intraureteric injection of dextranomer/hyaluronic acid copolymer. However, this form of antireflux surgery has not been tested in large randomized controlled trials. A randomized comparison of antibiotic prophylaxis with placebo (the RIVUR trial) showed a reduction in symptomatic infections, but no difference in the development of new scars, with antibiotic prophylaxis. Eradication of asymptomatic infection in children with or without proven vesicoureteric reflux used to be widely practised in the hope that it would prevent ascending infection and renal damage. However, prophylactic treatment for 2 years of covert bacteriuria in schoolgirls without renal scarring has no effect on glomerular filtra- tion rate at age 18, but was associated with lower fractional reabsorp- tion of glucose and with a smaller increment in glomerular filtration rate and greater degrees of glycosuria during subsequent pregnancy. Screening for asymptomatic bacteriuria with the aim of preventing these minor abnormalities is not currently thought justified. Pooled analysis of recent trials that have included a placebo arm show no clear evidence of benefit from long-term prophylaxis, either in terms of reduction of symptomatic UTIs or in reduction of the acquisition of new cortical scars. Fig. 21.13.5 Reflux nephropathy on intravenous urography, more marked on the right side than the left. Several focal scars (arrowed) involving the full thickness of the renal parenchyma and associated with

calyceal clubbing are most obvious in the polar regions. Reproduced with permission from Bailey RR (1993). Vesicoureteric reflux and reflux nephropathy. In: Schrier RW, Gottschalk CW, eds. Diseases of the kidney, 5th edn,
pp 689–727. Little, Brown, Boston. Copyright © 1993 Lippincott, Williams & Wilkins.

section 21 Disorders of the kidney and urinary tract 5090 Whatever the cause of reflux nephropathy, there is little doubt that women with it are more prone to recurrent acute pyelonephritis than those with anatomically normal upper urinary tracts, particu- larly during pregnancy. Invasive/destructive renal parenchymal infection As discussed previously, ascending infection may cause the clinical syndrome of ‘acute pyelonephritis’ but seldom causes significant renal parenchymal damage. However, this is not the case if there is further impairment of host defence against infection, particularly by diabetes or urinary tract obstruction. Acute papillary necrosis This is an unusual complication of acute pyelonephritis, but more likely to occur in older people and especially those with diabetes. It should be suspected, as should urinary stones, in the patient with symptoms and signs of acute pyelonephritis who also has pain sug- gesting renal colic. This situation requires immediate imaging, usu- ally with ultrasonography, to exclude urinary obstruction, and if obstruction is present then it must be relieved urgently, most often by antegrade nephrostomy. The use of NSAIDs is associated with an increased incidence of chronic renal papillary necrosis, perhaps because they compromise the renal medullary circulation. It therefore seems reasonable to say that these agents should be discontinued, at least temporarily, in the presence of acute pyelonephritis. Renal carbuncle or abscess Renal carbuncle is the formation of renal cortical abscesses, often only in one kidney, caused by blood-borne infection, usually asso- ciated with untreated S. aureus septicaemia. It is most commonly seen in intravenous drug abusers and patients with diabetes. There is usually a significant time delay between the initial infection and presentation with renal carbuncle, typically 6 to 8 weeks. Presenting symptoms include fever, malaise, and abdominal or flank pain, and are often nonspecific. Because the infection is limited to the renal cortex and does not communicate with the collecting system, the urine is sterile and acellular. Blood cultures are usually negative. Radiological studies show a semisolid, thick-walled mass, percutan- eous aspiration of which yields pus. Pyonephrosis Pyonephrosis is a bacterial infection within a completely obstructed collecting system, for instance, due to an obstructing ureteric stone. Patients usually present with fever, rigors, and flank pain, and have a marked neutrophilia and acute-phase response. Radiological differ- entiation from hydronephrosis relies on the presence of echogenic material and/or septa in the pelvicalyceal system, and confirmation is by percutaneous aspiration; as with other localized UTIs, the voided bladder urine may be sterile. Untreated pyonephrosis rapidly results in complete destruction of the renal parenchyma, followed by death from complications of sepsis if nephrectomy is not per- formed; correction of obstruction and aggressive intravenous anti- biotic therapy may prevent this if instituted soon enough. Perinephric abscess Perinephric abscess may complicate renal carbuncle or, more com- monly, acute pyelonephritis—particularly if complicated by an anatomical or functional abnormality of the urinary tract. Typical presenting symptoms are those of acute pyelonephritis, with flank pain, fever, and rigors. If the abscess does not communicate with the collecting system (e.g. in abscesses caused by haematogenous spread or complicating obstruction or renal cysts), there may be no lower urinary tract symptoms, no pyuria, and the urine may be sterile. Response to antibiotic treatment is much less rapid than in patients with uncomplicated acute pyelonephritis. Diagnosis is by ultra- sonography, urography, or CT, followed by percutaneous (or occa- sionally surgical) aspiration, drainage, and culture of the aspirate. Prolonged antibiotic treatment of the organism identified is needed, stopping only when

there is evidence that the infection has resolved, based on resolution of fever and of the acute-phase response, and re- peated radiological studies. This may take as long as 8 weeks. Xanthogranulomatous pyelonephritis Xanthogranulomatous pyelonephritis is an atypical form of chronic infection of the renal parenchyma in which bacterial infection, usu- ally in the presence of obstruction or staghorn calculi, results in for- mation of granulomas with the accumulation of lipid-rich foamy macrophages. The process may be multifocal and can be complicated by extension into the perinephric fat, causing perinephric abscess. Patients are typically febrile and ill, with a history of progressive weight loss, anaemia, and malaise, without lower urinary tract symp- toms, and have a mass in the flank on examination. Radiologically, the multifocal mass crossing tissue planes may be indistinguishable from a renal cell carcinoma, which may also cause systemic symp- toms such as fever, anaemia, and weight loss. Although both require surgical excision, radical surgery can be avoided if the diagnosis is made preoperatively. Emphysematous pyelonephritis Emphysematous pyelonephritis is a rare and life-threatening form of acute pyelonephritis in which there is tissue necrosis together with formation of hydrogen and CO2, which accumulate in pockets in the renal parenchyma, perinephric space, and collecting systems— ‘gas gangrene of the kidney’ (Fig. 21.13.6). The typical patient is an Fig. 21.13.6 Gas-forming infection, seen as the three black holes in the single remaining (right) kidney of a patient with diabetes. The left kidney had been removed 2 years earlier for a similar gas-forming infection. This infection was successfully treated by intravenous antibiotics and percutaneous drainage.

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